Decision Memo for Electrodiagnostic Sensory Nerve Conduction Threshold (CAG-00106R)

Decision Summary

Based on the evidence as a whole, CMS concludes that the use of any type of s-NCT device (e.g., "current output" type device used to perform CPT, PPT, or PTT testing or "voltage input" type device used for v-NCT testing) to diagnose sensory neuropathies or radiculopathies in Medicare beneficiaries is not reasonable and necessary. Therefore, CMS intends to maintain its national noncoverage policy for sensory-Nerve Conduction Threshold testing.

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Decision Memo

(This decision memorandum does not constitute a national coverage determination (NCD). It states CMS's intent to issue an NCD. Prior to any new or modified policy taking effect, CMS must first issue a manual instruction, program memorandum, CMS ruling or Federal Register Notice, giving specific directions to our claims processing contractors. That issuance, which includes an effective date, is the NCD. If appropriate, the Agency must also change billing and claims processing systems and issue related instructions to allow for payment. The NCD will be published in the Medicare Coverage Issues Manual. Policy changes become effective as of the date listed in the transmittal that announces the Coverage Issues Manual revision.)

TO: Administrative File: CAG-00106R Reconsideration of Coverage Issues Manual Section: 50-57.1 Current Perception Threshold/Sensory Nerve Conduction Threshold (s-NCT) Test

From:

Steve Phurrough, MD, MPA
Acting Group Director, Coverage and Analysis Group

Carlos Cano, MD
Acting Director, Division of Items and Devices

Ronald Dei Cas, MD, FACS
Medical Officer, Division of Items and Devices

Lorrie Ballantine
Health Insurance Specialist, Division of Items and Devices

Tanisha Carino, PhD
Health Insurance Specialist, Division of Operations and Committee Management

Subject: Decision Memorandum for Reconsideration of National Coverage Determination: Sensory Nerve Conduction Threshold Testing

Date: July 8, 2003

This memorandum responds to a request that CMS reconsider a national coverage determination that was effective on October 1, 2002. This memorandum serves five purposes: (1) describes sensory nerve conduction threshold (s-NCT) testing; (2) describes two devices currently marketed for sensory nerve conduction threshold testing (i.e., the Neurometer©, a type of current output sensory nerve conduction threshold test, and the Medi-Dx 7000©, a type of voltage input sensory nerve conduction threshold test (v-NCT); (3) reviews the history of Medicare's coverage of sensory nerve conduction threshold testing; (4) analyzes and presents relevant scientific and clinical literature on the use of both types of s-NCT devices for the diagnosis of peripheral sensory nerve and nerve root conditions and how information provided by each device affects the management of patients with peripheral sensory nerve or nerve root abnormalities; and, (5) delineates the reasons for maintaining a national non-coverage determination for s-NCT (including both the current output and voltage input type devices).

I. Background

Sensory nerves gather information (via dendritic processes) on various types of sensation and conduct that information (via axons) by electrical impulses to the spinal cord and the brain. In the brain this information is processed and interpreted. The axons that direct these sensory impulses from the periphery to the brain are bundled together by connective tissue into cords called fibers. Some fibers are surrounded by a protective coating called myelin; much like insulation around a wire. In general, fibers that are myelinated conduct their impulses more quickly. This variability in conduction velocity is manifest by separate classes of fibers that are generally thought to conduct different sensory information. There are three types of generally recognized sensory nerve fibers:

(1) A-beta fibers, the largest diameter fibers, are myelinated and conduct nerve impulses the fastest of the three sensory fiber types. They are thought to conduct sensations of touch, mild pressure and vibration;

(2) A-delta fibers are smaller than A-beta fibers, but are also myelinated. They conduct impulses at a slower rate than A-beta fibers, but at a faster rate than the C fibers. A-delta fibers are thought to conduct cold temperature sensation and one component of pain (i.e., "fast" pain); and
(3) C fibers, the only unmyelinated of the sensory fibers, are also the slowest and smallest of the three fiber types. They are thought to conduct the sensation of warmth and another component of pain (i.e., "slow" pain). They also provide most neural input to the autonomic nervous system.

Several disease processes affect the peripheral sensory nervous system. A non-exhaustive list includes: metabolic diseases such as diabetes and uremia; toxic/nutritional disorders such as lead poisoning, alcohol abuse and various vitamin deficiencies; hereditary disorders such as Fabry's disease; autoimmune diseases such as chronic inflammatory demyelinating polyneuropathy; acquired compressive conditions such as carpal tunnel syndrome; and occupational disorders such as Hand-Arm Vibratory Syndrome.

Traditionally, the clinical assessment of sensory nerve function consists of history and physical examination with or without additional testing. The methods currently employed to test sensory nerve function include nerve conduction studies (NCS), sensory nerve biopsy, and quantitative sensory nerve testing (QST). Laboratory tests (i.e., fasting blood glucose, heavy metal levels, and various antibodies) may also provide important diagnostic information.

NCS can be used to detect both motor and sensory nerve function. In NCS a skin electrode provides a neural stimulus (via an electric shock) and a more distally placed electrode records information from the resulting action potential (e.g., conduction velocity, latency of response, and amplitude of response). This information can help to determine diagnosis, severity, location, and distribution of a neuropathy, and can also assess the integrity of the axon and its myelin sheath. In general, sensory NCS measure primarily fast fibers. Although the test is not invasive, it does cause the patient discomfort.

Sensory nerve biopsy is an infrequently used method of assessing sensory nerve disorders. It involves biopsy of a cutaneous nerve, typically the sural nerve. This can give information on the extent of axonal degeneration and of segmental demyelination. It is most useful in assessing certain systemic illnesses such as amyloidosis, sarcoidosis, leprosy and vasculitis.

Quantitative sensory testing (QST) involves psychophysical tests that are performed to provide a quantitative value to the subjective feelings of sensation: touch-pressure, vibration, cooling, warming, and pain. QST, like such well-known tests as visual acuity testing and audiometry, involves graded stimuli presented to a physical area (e.g., skin in nerve conduction threshold tests) and a psychological component (e.g., the mental recognition of the stimulus). The threshold is the smallest stimulus magnitude that is recognized when testing for decreased sensation or the maximum stimulus tolerated when testing for pain tolerance. QST differs from the sensory tests commonly used in physical examination (i.e., pinprick, cotton swab) in that QST allow for the derivation of a graded, quantifiable response from the patient. Examples of QSTs include the 128 Hz Reidel Sieffert graduated tuning fork for vibratory testing, the biothesiometer for vibratory testing, the thermoaesthesiometer for thermal testing and the Semmes-Weinstein monofilament for touch sensation.

There are two types of Sensory Nerve Conduction Threshold (s-NCT) testing devices. One works on a "current output" paradigm and the second uses a "voltage input" paradigm. The former type is the most extensively studied type of s-NCT device and is also referred to as Current Perception Testing (CPT). Hereafter in this decision memorandum whenever the term CPT is used it will refer to the "current output" type of s-NCT device. The latter type of device, the one that works off a "voltage input" paradigm, is termed voltage-nerve conduction threshold testing and is referred to herein as v-NCT. Although the physics and engineering behind the devices differs, they each act to provide quantitative data on sensory nerve conduction threshold.

As noted above the "current output" type of device is generally termed CPT testing and is performed to determine the minimum stimulus that evokes a sensation. The same device, however, can also be used to detect the minimum stimulus that evokes pain or the maximum stimulus that can be tolerated. When it is used to determine the minimum stimulus that evokes pain the test is termed the Pain Perception Threshold (PPT) and when used to determine what the maximum stimulus that can be tolerated is it is termed the Pain Tolerance Threshold (PTT). All three tests (CPT, PPT, and PTT) involve the same testing methodology with the same device and only differ in the response sought from the patient. It is a non-invasive test typically conducted by technicians under the supervision of a physician. Disposable surface electrodes are placed on the patient's skin in a desired location. Mild electrical stimuli are applied to the skin via these electrodes and the metered current output is responsible for the response generation. Measures are obtained using a portable, 6-V battery powered, microprocessor that produces controlled, constant alternating current at intensities ranging from 0.01 mAmperes to 9.99 mAmperes and frequencies of 5 Hz, 250 Hz, and 2,000 Hz. These three frequencies are meant to correspond to the frequencies thought to be selective for the C, A-delta, and A-beta fibers respectively. A forced-choice[1] protocol is used and after an initial tentative threshold is determined, stimuli are presented that vary around this presumed threshold to confirm threshold stability. Therefore, threshold determination requires a consistent patient response. Testing time is around 15-20 minutes. The manufacturer states that the test is currently delivered in a double blind manner, which means that the patient and the person administering the test do not know the amplitude of the stimulus frequency being delivered. It is unclear if the test has always been delivered double blind. Some of the early articles reviewed herein describe the test as a single blinded test, meaning only the patient was unaware of the amplitude being delivered.

The alternative s-NCT device, which relies on a "voltage input" paradigm, is the v-NCT device. It is a measure of the voltage intensity entering the body that elicits the patient response. As noted in the FDA section, the predicate device upon which the v-NCT machines were compared was the CPT. The v-NCT device also can test at 5, 250 and 2000 Hz. The testing paradigm is single blind (only the patient is unaware of the amplitude being delivered). The manufacturers of each device (CPT and v-NCT) have stated that their respective devices operate through fundamentally different mechanisms and should not be compared to one another. Both devices, however, are a type of s-NCT and, therefore, this memorandum applies to both of them. However, CMS will review each device independently and make separate reasonable and necessary determinations.

The most common CPT device is the Neurometer® manufactured by Neurotron, Inc. The only v-NCT device currently on the market is the Medi-Dx 7000© manufactured by Neuro-Diagnostic Associates.

A list of definitions for the abbreviations used in this decision memorandum can be found in appendix 1.

II. Food and Drug Administration (FDA) Status

Neurotron received FDA 510(k) clearance in 1986 to market the electrodiagnostic sensory Nerve Conduction Threshold s-NCT/CPT Neurometer® for the evaluation of sensory nerve diseases and injury. A 510(k) is a premarketing submission made to the (FDA) to demonstrate that the device to be marketed is substantially equivalent to a legally marketed predicate device that is not subject to the more extensive premarket approval. The predicate device (found to be substantially equivalent) to the s-NCT/CPT was the vibratory end-organ tester.

Neuro-Diagnostic Associates received FDA 510(k) clearance to market the Medi-Dx 7000 device in 1997. The predicate device (found to be substantially equivalent) to theMedi-Dx 7000 was the Neurometer®. It should be noted that in the manufacturer's 510 (k) summary statement to the FDA (submitted prior to their device receiving 510 (k) clearance to market), the company stated, "The Medi-Dx 7000 and the equivalent (Neurometer) device are essentially the same, they weigh the same and are approximately the same size."

However, Neuro-Diagnostic Associates has told CMS that their device is not the same as the Neurometer® and should be considered separately. First, CPT testing uses a sinusoidal wave form and, according to the Medi-Dx 7000 manufacturer, this provides a small "window" for the nerve threshold to which the patient can respond. Second, the close proximity of the electrodes used in CPT testing can affect the depth with which the current extends into the skin causing only superficial nerves to be affected. Third, they stated that the skin's electrical impedance is constantly changing and this can impart unpredictability to the CPT results. Neurotron, the manufacturer of the most commonly used CPT device (Neurometer®) has addressed each of these concerns in separate conversations with CMS and maintains that such criticisms are unfounded. While such differences between the machines may or may not be physically and/or clinically important, CMS's concern is with the merit of the evidence surrounding each device and how each device can affect net health patient outcomes in Medicare beneficiaries. Also at this meeting, Dr. Cork stated that he only tests at the 250 Hz frequency and did not believe that testing at 5 or 2000 Hz was clinically useful, in part because he was not convinced that different nerve fiber types could be independently tested. Finally, the manufacturer informed CMS that studies to investigate interobserver reliability testing with their device have not been performed.

It is our intention to review the evidence on each device separately in this decision memorandum concerning sensory nerve conduction threshold testing.

III. History of Medicare's Coverage Policy on Nerve Conduction Threshold Testing

On February 14, 2002 Medicare published a decision memorandum announcing our intention to issue a national noncoverage policy with regard to the use of s-NCT/CPT devices in the evaluation and diagnosing of sensory neuropathies and other sensory impairments. This policy became effective on October 1, 2002.

Timeline of Activities

November 1, 2002	Formal request for reconsideration submitted by Neurotron, Inc., the manufacturer of the Neurometer® (a CPT device) accepted by CMS.
January 15, 2003	Neuro-Diagnostic Associates, Inc., the manufacturer of Medi-Dx 7000, a voltage sensory nerve conduction threshold testing device, stated that their device is substantially different than the CPT device. To accommodate their concern, and to allow for comments on this issue, CMS extended the deadline to February 21, 2003.
February 11, 2003	At the request of Neuro-Diagnostic Associates, CMS met with their President and CEO, Dr. James Hedgecock, PhD, and Randall Cork, MD, PhD, one of the primary clinical investigators of the Medi-Dx 7000. At that meeting the manufacturer stated to CMS that their Medi-DX 7000 device differs from CPT testing in several respects.

Benefit Category Determination

The benefit category appropriate for the s-NCT is set forth in section 1861(s)(3) of the Social Security Act (s-NCT is a diagnostic test).

Coding

The proper coding for sensory nerve conduction testing (whether using the "current output" or "voltage input" types of devices) is G0255. The use of the codes for nerve conduction testing, amplitude and latency/velocity study (e.g., 95900, 95903 or 95904) for this service are inappropriate. Sensory nerve conduction threshold testing does not provide information on the nerve conduction, amplitude, latency, or velocity of the nerve response, and, thus, cannot be described using a code that specifies such information.

IV. General Methodological Principles

When making national coverage determinations, we generally evaluate relevant trials to determine whether or not the data is of sufficient quality to support a conclusion that the technology is reasonable and necessary. CMS considers generally accepted methodological principles when assessing clinical trials for diagnostic tests or therapeutic interventions. When CMS reviews a diagnostic test for a national coverage determination, staff considers the validity of study results and the accuracy of the test in distinguishing patients with or without the target disorder. We then determine the usefulness of the test for patient management (42 C.F.R.§ 410.32).

Valid clinical studies minimize bias in their study design. Bias is any systematic error in design, conduct or analysis that results in mistaken estimate of results. Patient selection is one type of bias that can occur. For a non -randomized study, the selection of the intervention group and the control group should be fully described in the study. Inclusion and exclusion criteria identifying the characteristics of the participants in the clinical study should be well defined. The presence of patients with comorbid conditions could alter the results of the study. For example, a diabetic that may also be an alcoholic needs to be identified, as alcohol use may affect nerve conduction study results. Randomization protects against inadvertent selection bias resulting in the unequal distribution of health status characteristics or confounding variables that would create dissimilar experimental and control groups from the start of the trial. The method of randomization or other group assignment method needs to be described so the reviewer can tell whether various baseline factors that may influence the study outcomes have been taken into account. Thus, comparability of the experimental groups at baseline is crucial to evaluate the outcomes of the study. The two groups need to be as homogenous as possible. If these groups are not alike, these characteristics need to be reported, and adjustments should be made in the statistical analyses of the results.

The optimal comparison in a study of a diagnostic test is between the test under review and the "gold standard." Ideally, patients should have undergone both the diagnostic test under study and the reference or "gold standard" test (e.g. a biopsy or some other observation proving that subjects do or do not have the target disorder). Blinding patients and investigators is an important aspect of this type of clinical study. Blinding refers to the process of ensuring that individuals involved in the trial and investigators interpreting the results do not know to which group (test under study or reference standard) the patients were assigned.

Sample size (number of patients in the study) is a critical aspect for clinical studies for two reasons. One is that we need to be able to generalize the results of the study to a broader population. If there are not enough patients in the study it is harder to generalize the results. The second reason why sample size is important is the ability to determine that the results of the study, whether positive or negative, were caused by the intervention being studied. Since random variation can be the source of observed differences in a clinical study, the sample size must be large enough to make chance occurrence an unlikely explanation for the results.

An important consideration in this review of sNCT is an assessment of the accuracy and technical characteristics of the test as compared to other diagnostic modalities. Accuracy refers to the ability of the test to distinguish patients who have or do not have the target disorder. Measures used to determine accuracy include sensitivity (probability of a positive test result in a patient with the disease) and specificity (probability of a negative test in a patient who does not have the disease). In assessing the accuracy of a test, one must always balance the test's sensitivity and specificity. This is because a highly specific test minimizes false positive results while a highly sensitive test minimizes false negative results. In many tests, however, increasing sensitivity or specificity is done at the expense of the other. However, even though a diagnostic test may be very accurate, if the information it provides does not alter the patient's management, CMS may determine that the test is not reasonable and necessary.

V. Summary of Evidence

The requestor for this reconsideration, Neurotron, Inc., was also the requestor for the decision memorandum that was issued February 14, 2002. Neurotron is the manufacturer of one type of s-NCT device, the Neurometer®. In a formal request for reconsideration, Neurotron provided a detailed rebuttal to our February 14, 2002 decision memorandum. In that rebuttal, Neurotron stated that CMS had failed to take into consideration all the available evidence on sensory nerve conduction testing and that we misinterpreted the evidence that was considered. To address these concerns CMS asked Neurotron to provide us with all the evidence they felt was available on s-NCT and a *de novo* review of all information, including that which had been reviewed in the February 14, 2002 decision memorandum, was undertaken.

For this reconsideration the requestor (Neurotron, Inc.) provided CMS with 342 articles and abstracts regarding the use of CPT. The manufacturer of the v-NCT device (Neuro-Diagnostic Associates) provided CMS with two articles concerning v-NCT use. In addition, the bibliographies of each of these articles were reviewed and a literature search was performed to identify additional resources. The literature search employed various combinations of the following search terms: “sensory nerve conduction threshold,” “Neurometer,” “current perception threshold,” voltage nerve conduction threshold,” “Medi-Dx 7000”, and “quantitative sensory testing.” No additional articles beyond those supplied by the manufacturers were identified.

CMS consistently applied broad guidelines to the total body of literature in order to determine which articles/abstracts to review. Three basic guidelines were used in selecting articles for review:

1) literature had to use either the CPT or v-NCT device on human subjects,
2) literature had to be published in English,
3) literature had to provide original research. As such, review articles that did not provide original research were excluded.

Applying these guidelines to the total pool of articles resulted in 59 articles being excluded because they were either not performed on human subjects (6), were review articles that provided no original research (23), or were not published in English (30). There were 238 abstracts or case reports that were not full text articles. All abstracts and case reports were reviewed and considered in this decision memorandum. They are not all discussed herein because they all provided limited methodologic description and, thus, a fair, written critique is difficult. This left, of the 342 articles submitted to CMS for review, a total of 44 full text articles on CPT that are reviewed herein. In addition to the above articles, CMS reviewed a technology assessment published in 1999 by the American Association of Electrodiagnostic Medicine (AAEM) that serves as an official position of this medical association. Finally, a summary statement on Quantitative Sensory testing by the American Academy of Neurology (AAN) published in the March 25, 2003 issue of *Neurology* is reviewed.

The available literature on v-NCT was limited to two articles supplied by the manufacturer.

Sensory-Nerve Conduction Threshold Testing using the Current Perception Threshold (or Pain Perception Threshold and Pain Tolerance Threshold) Test

Normal Values

In investigating the efficacy of CPT there should be reference standards against which to compare this device (or longitudinal studies that demonstrate that diagnoses noted on CPT actually develop in the patients tested). There should also be defined normal CPT values for healthy subjects. Without established normal values there is no consistent internal reference by which CPT values can be compared.

The requestor provided CMS with mean CPT values from healthy subjects (see table below). The data were broken down by body site and frequency, and were culled from studies performed in various countries. The numbers in parentheses are the standard deviations.

CPT Frequency	**Face**		**Finger**			**Toe**		
		USA	Korea	USA	Japan	Taiwan	USA	Taiwan
5 Hz	10 (10)	11 (8)	46 (27)	61 (30)	50 (25)	73 (34)	74 (30)	

CPT Frequency	Face		Finger			Toe		
		USA	Korea	USA	Japan	Taiwan	USA	Taiwan
250 Hz	19 (14)	21 (12)	81 (42)	93 (44)	78 (30)	125 (52)	126 (50)	
2000 Hz	118 (52)	99 (28)	226 (80)	236(62)	230 (70)	322 (110)	325 (106)	

The USA values were obtained from research conducted at several institutions. It is unclear if these data were obtained in a systematic program for establishing normative values[2]. The data from Korea, Japan, and Taiwan come from separate, published studies and are discussed below. The requestors did not provide information on whether the different normal values at the varying frequencies and sites were statistically similar between the countries. It should also be noted that the standard deviations show a very wide range of normal values around the means.

The study by Kim et al (2000) and the study by Takekuma et al (2000) raise interesting questions regarding normal CPT values. Kim et al studied 25 healthy Korean subjects as part of their test of CPT reliability and 200 additional healthy subjects as part of their study on the effects of age and gender on CPT measurements. They only tested facial sites and not finger or toe sites[3]. The intra-rater reliability ranged from .76 to .95 while the inter-rater reliability was much more variable ranging from .46 to .87, a surprising finding for a test delivered in a double-blind fashion. Kim et al did not find a difference in CPT measurements with gender or age. The authors noted that "it is critical that the subject focus on the stimulus" and that the greatest source of error in CPT testing is "lack of attention by the subject" (Kim et al, p.290). The reliability measurements were performed on 25 subjects with a mean age of 23.6 years.

Takekuma et al investigated age and gender differences in CPT measurements in 1632 Japanese subjects. The subjects were part of a larger longitudinal study on aging and were stratified; random samples of community-dwelling Japanese aged 40 to 79. High intra-rater and inter-rater correlation coefficients were noted (.95 to .97, and .86 to .98 respectively). These high correlations are in contrast to the values noted by Kim et al. However, Takekuma and co-authors did not state how many subjects were retested, how many times they were retested, nor the time between retests. Takekuma et al also reported gender and age differences for some measurements. At 250 and 5 Hz, women showed lower CPT measurements than men although there was no difference at the 2000 Hz stimulus. Age variations were seen for both men and women at the 2000 and 250 Hz level, but only men showed a difference with age at the 5 Hz level.

Takekuma et al noted limitations with their study. A detailed neurological examination was not done on subjects to rule out neuropathologies. Also there was limited training for those who performed the CPT test. It should be noted that Takekuma stated they undertook this study because "there have been only a limited number of reports which investigated CPT values in community-dwelling people, (and) little is know about variations with age and gender" (Takekuma 2000, p. S-33). This statement is interesting given that this comes from a 2000 publication and, thus, calls into question the validity of the normal values used in the various studies reviewed in this decision memorandum.

Katims et al (1987) also provided information on normal CPT values. In this study, Katims performed CPT on 60 healthy volunteers[4]. They noted a slight but statistically significant sex difference on finger CPT values. The also found that the only statistically significant effect of age on CPT measurements was seen in the facial thresholds. This differs not only from the findings of Takekuma (above), but also from the findings of an earlier study (Katims et al, 1986). In that study, an effect of age was noted with the 2000 Hz stimulus at toe and facial sites.

The 1986 study by Katims et al (noted above) obtained CPT data on 44 normal control subjects (median age 53 years, range 32-87)[5]. Those older than 53 years had significantly elevated CPT measurements on the 2000 HZ stimulus at the toe and face as compared to younger subjects. No mention of gender differences was made. It was not stated if the difference at the 5 Hz stimulus level was significant. It does not appear from this study that the subjects were tested with the 250 Hz stimulus.

Evans et al (1992) provided data on how CPT values varied with aging in normal individuals. The authors studied 39 healthy elderly (i.e., > 65 years) and 30 healthy young (i.e., <35 years) individuals using CPT. Measurements were taken in the feet, hands, and face with the three standard CPT stimuli. The authors found that there was no significant difference in CPT measurements at any site and at any frequency between the young and old group. Thus, Evans et al concluded that CPT measurements do not change with age.

Lerner et al (2000) investigated the reliability and reproducibility of CPT in testing sensation in the mental foramen area in 34 healthy volunteers. The subjects were tested on their right and left sides with the three standard testing frequencies. The subjects were then retested by the same operator between 7 and 153 days after the first test. The side to be tested first was chosen randomly. It is not stated if the person administering the test was masked to the results of the first test when performing the second. The authors stated that there was no significant difference between the first and second test on the left side ($p>.05$), but there was a significant difference between the first and second tests on the right side (no p value given). The authors, however, stated that the confidence intervals for the right-sided tests were narrow and the difference was not clinically significant. How they measured, and what constituted, clinical significance was not discussed.

The final country from which the requestor provided us with normative data was Taiwan. These values came from the study by Ro et al (1999) in which CPT was performed on 50 healthy volunteers and 16 patients with Fabry's disease. The mean age of the 50 healthy subjects in this study was 34.5 ±9 years. In the published article the normative values were not listed nor was there any discussion of the differences in normative values between different testing sites, stimulus frequencies, or age/gender differences.

Studies Investigating the Diagnostic Accuracy/Patient Management Information Provided by CPT, PPT, and PTT

Thirty-seven articles that investigated the use of CPT (or PPT, PTT) in the diagnosis of some type of neuropathology were identified. CMS used the inclusion guidelines noted above when selecting the articles for this review. Two of the necessary inclusion guidelines were direct comparison to another diagnostic modality or information on how the test data affected patient management. However, in an effort to be as inclusive as possible, we employed a broad interpretation of what constituted direct comparison or information on patient management. Limitations of the studies are noted where applicable. The following summary of the evidence divides the articles into the general topic areas covered. There were 15 articles that investigated the use of CPT in diabetic polyneuropathy, five that used CPT in some form of study involving analgesia, four that investigated neuropathy in patients undergoing hemodialysis, three that involved carpal tunnel syndrome, two each that investigated the use of CPT in hand-arm vibration syndrome and intervertebral disc disease, and six that covered miscellaneous clinical concerns. Within each of the following headings the articles are presented alphabetically by lead author.

Diabetic polyneuropathy

Cheng et al (1999) studied 558 Chinese subjects with type II diabetes to identify risk factors for diabetic peripheral neuropathy. All subjects (mean age 61±10 years, 52% male) were given three quantitative sensory tests (QST) - monofilament testing, tuning fork, and CPT. Subjects who had a positive result on at least two of the three QSTs were diagnosed with peripheral neuropathy. There was no attempt to correlate these QST findings with symptoms or physical exam. Sixty-two (11%) patients had at least two positive QST results. The authors stated that monofilament testing was positive in 59 (10.6%) subjects, tuning fork was positive in 45 (8%), and CPT was positive in 189 (34%). Cheng and co-authors, however, did not state how many of these 59, 45, and 189 patients were ultimately confirmed to have peripheral neuropathy through a second, confirmative test. In addition, it is not clear that the method they used for deciding who had peripheral neuropathy was a standard method for such diagnosis. Thus, it is not possible to determine the sensitivity/specificity for any of these tests.

Donaghue et al (1995) examined variables in functional measurements of three sensory nerves (superficial peroneal, sural, and posterior tibial) in neuropathic diabetic patients and compared them to measurements in non-diabetics. Sixty-one type I diabetics (mean age 55 years, mean duration of diabetes 24 years) and 66 age and sex-matched non-diabetic subjects were included in this study. CPT evaluations were performed over the three above-listed nerve distribution sites at 250 Hz. In addition, all patients were assessed using a neuropathy symptom score (NSS), neuropathy disability score (NDS), vibration perception threshold (VPT), and monofilament testing. Using the NDS to define the severity of neuropathy, the authors reported that mild, moderate and severe neuropathy was present in 13%, 54%, and 33% of patients. The authors stated that the NSS they used was a modified version of one described and validated by Dyck,[6] however, their modified version's validation was not described. In addition, they did not state if the NDS used had been previously validated. Thus, it is unclear if either score employed had been independently validated as a measure of neuropathy severity. The authors reported that in both the diabetic and non-diabetic subjects, CPT values of the posterior tibial nerve were higher than at the other two nerves. They also reported that CPT measurements between the two feet at all three nerve sites tested were not significantly different in either the diabetic or non-diabetic subjects.

There are a number of issues that need to be addressed regarding this study. First, there is limited information on the methodology used for patient selection. Second, the authors gave no explanation for why CPT was performed only at the 250 Hz level. Also, the authors stated that all diabetic subjects had neuropathy but did not state how this was diagnosed. The authors stated, "all subjects were tested by two examiners who worked very closed and used the same techniques"(p.38). It is unclear if this means the examiners were masked and, if masked as to the presence of neuropathy or diabetes, to what level. In addition, the study did not provide evidence that CPT can accurately diagnosis patients with neuropathy and at what severity level. The authors provided no correlation of NDS scores and CPT measurements. In the discussion section of the paper the authors wrote, "in view of the high variability of the quantitative sensory testing one measurement alone of any of the available techniques may not be sufficient in evaluating diabetic neuropathy and may lead to erroneous results" (p.40). They concluded that "for the accurate diagnosis of diabetic neuropathy multiple sites and more than one test (i.e., QST) should be employed" (p.41).

Katims et al (1986) was discussed, in part, earlier in the section on normal CPT values. In addition to the information on 44 normal individuals, the authors also provided data on 33 diabetic subjects. According to the authors, a neurological examination revealed that most of the 33 diabetic subjects possessed a mild to moderately severe peripheral neuropathy. What was meant by "most" was not defined. Also, the authors did not state the extent of neurologic examination nor what tests were employed. The subjects had CPT measurements taken at toe, finger, and facial sites at 2000 Hz and 5 Hz. There was no information on the 250 Hz stimuli, despite the fact that 250 Hz stimuli is one of the three generally used frequencies. The authors stated that the best sensitivity for detecting peripheral neuropathy was 94% when measurements from the two frequencies and all three sites were combined. Despite the fact that this study also included data from 44 normal subjects, there was no direct comparison of the CPT values from the normal and the diabetic subjects. Also, the raw data was not reported, making the reader rely on the reported sensitivity. The authors did not state exactly how many of the 33 patients had peripheral neuropathy and did not state how many of these tested positive and negative with CPT. Thus, it is not possible for CMS to independently validate this reported sensitivity. In addition, there was no information on the test's specificity. A high sensitivity in the face of low specificity means the test may yield a higher number of false positives as compared to false negatives. Finally, there was no information on how patients were selected nor was there any discussion of whether those administering the test were masked to the physical exam findings.

Katims et al (1987) was discussed, in part, earlier in this memorandum under the section on normal values. In addition to performing CPT on 60 normal control subjects, the authors in this study also tested 34 diabetics with varying degrees of neuropathy, 29 individuals enrolled in an alcohol detoxification program, and 11 subjects with various forms of non-diabetes-related neuropathy. In the 34 diabetic subjects with neuropathy there was a dramatic increase in CPT values as compared to the normal volunteers and this was most marked in the toe at 250 Hz. Changes of a lesser magnitude were noted in the subjects enrolled in the alcohol detoxification program and in the non-diabetic neuropathy groups. There was no information on how patients were selected for this study nor was there any information on whether the observers were masked to the underlying diagnoses. It is unclear from the methodology description if the test was delivered in a single-blind fashion (the observer knew the amplitude of the stimulus being delivered) or a double-blind manner (neither the patient nor the observer knew the amplitude of the stimulus being delivered). As stated earlier in the Background section of this memorandum, the manufacturer currently states that the test should be performed in a double-blind manner. There was also no information on how patient diagnoses were confirmed. Finally, there was no diagnostic modality to which CPT was compared; thus, it is not possible to assess the diagnostic accuracy of CPT from this study.

Kempler et at (1995) stated that the aim of their study was to examine autonomic and sensory function in patients with established non-insulin dependent diabetes (NIDDM) and those with newly diagnosed NIDDM (ND-NIDDM). They reported data on 22 patients with NIDDM, six with ND-NIDDM, and 12 controls. Information on how patients were selected was not given. CPT testing at 5, 250, and 2000 Hz was performed on all subjects over the median and peroneal nerve distributions. The authors reported that at 2000 Hz the CPT values for both NIDDM and ND-NIDDM subjects were significantly elevated at the median and peroneal nerve sites. At 5 Hz the CPT values for the NIDDM subjects were significantly elevated relative to controls only at the peroneal site. Later in the article, however, the authors noted that in the ND-NIDDM subjects the median nerve sites all tested within the normal range, albeit at statistically higher normal values than the controls. No data were presented on the results obtained at the 250 Hz stimuli for either the median or peroneal nerve sites.

There were basic methodologic problems with this article, such as details on patient selection and masking of observers to patient diagnosis, study hypothesis, and other test results. Also, there is no correlation of the CPT findings with either symptoms or physical exam. Also, in order to prove that CPT can diagnosis diabetic neuropathy at a point before it is manifested clinically (and in absence of another modality that can act as a reference standard), the authors need to follow patients with abnormal CPT results and no clinical neuropathy longitudinally and demonstrate that such patients indeed manifest neurologic changes. Thus, this article's conclusion that CPT permits the diagnosis of sensory dysfunction early in the course of diabetes was not demonstrated.

Masson and Boulton (1991) in the Symposium Proceedings section of the journal *Diabetic Medicine* published an article that was both a review of CPT and also contained information on a preliminary evaluation of CPT testing on 22 normal control subjects and 59 diabetic patients with and without conventionally defined neuropathy. Subjects were tested with CPT over the distribution of the median and peroneal nerves at 5, 250 and 2000 Hz. The authors reported that for all frequencies there were significant differences between the normal and neuropathic patients although actual data with significance values were not given.

This study had many methodological flaws. There was no information on patient selection criteria, patient demographics, or observer masking. The authors did not discuss how patients were assessed for neuropathy or how many had evidence of neuropathic changes. In addition, there were very limited data presented. It is interesting that in the introduction to this paper the authors wrote, "the manufacturer's literature describes this device as the new gold standard for peripheral nerve testing but this claim is made without the proper large-scale independent test data."[7]

Masson et al (1989) investigated the use of CPT for the assessment of peripheral neuropathy in patients with type I and type II diabetes. The study included 90 diabetic patients and 31 control subjects. The diabetic patients were divided into three groups: 1) those without neuropathy, 2) those with neuropathy, and 3) those with neuropathic ulcers. A cohort of 68 patients also had conventional assessment of peripheral nerve function using two other QSTs - biothesiometer (to test vibration perception) and thermoaesthaesiometer (to test warmth perception). The 31 controls ranged in age from 19-82 years and the 90 diabetic subjects ranged in age from 18-79. CPT measurements were significantly different between the neuropathy group versus the control group ($p < .05$). The CPT measurements in the ulcer group were also significantly different from the control ($p < .001$) as well as the diabetics without neuropathy group ($p < .001$). The authors also reported that there was significant correlation between the findings of CPT at 2000 HZ and the vibration QST (large fiber test) and between the 5 Hz stimuli and the thermal QST (small fiber test).

Despite these results, this study by Masson et al leaves some questions unanswered. First, it is not clear how diabetic neuropathy was diagnosed. Thus, it is not possible for CMS to conclusively determine the accuracy of CPT in diagnosing peripheral neuropathy. Also, it was not stated how patients were selected for this study nor if the observers were masked to the results of the different tests. Finally, and most importantly, the scatterplots provided demonstrated that there was considerable overlap in CPT values between the control patients and all three groups of diabetic patients at the three CPT stimuli frequencies tested. As noted earlier, this is important because large overlaps of values, even if the differences were reported to be statistically significant, calls into question the confidence one can place in such reported differences.

Olmos et al (1995) investigated the use of Semmes-Weinstein Monofilament (SWM) testing and CPT as a predictor of foot ulceration in patients with NIDDM. The authors enrolled ambulatory patients with NIDDM from their diabetes clinic. Patient selection methodology and inclusion/exclusion criteria were detailed. The patients were divided into two groups. Group one was comprised of 168 patients with no current or past foot ulcer and group two was comprised of 14 patients with either an active foot ulcer or a history of foot ulcers within the preceding 12 months. Patients had SWM testing at three points on their feet while CPT measurements were done over the distribution of the peroneal nerve (great toe) at 5, 250 and 2000 Hz frequencies. The authors found that both the SWM and CPT tests (at all frequencies) were significantly different in the foot ulcer as compared to the no foot ulcer groups. There was no information on how the SWM and CPT tests compared to each other. This study was not masked and the two tests were not compared to each other nor to another diagnostic modality. As such it is not possible for CMS to make conclusions regarding the diagnostic ability of either CPT or SWM in diabetic foot ulcers.

The study by Pitei et al (1994) was undertaken to assess the ability of CPT to distinguish between different types of nerve fiber damage using different stimulus frequencies. The authors compared the results with standard sensory tests, VPT, and warm and cold TPT. The authors studied 51 patients with diabetes and 28 age and sex-matched non-diabetic controls. All 51 diabetics had evidence of neuropathy including 26 with recurrent foot ulcers and 13 with evidence of bone and joint destruction. CPT testing was done bilaterally on the index finger (median nerve) and great toe (peroneal nerve) of all subjects at 5, 250 and 2000 Hz. VPT testing was also done bilaterally using a biothesiometer at the tip of the hallux and distal aspect of the index finger. Warm and cold TPT was done on the palmar surface of both hands and the dorsal surface of both feet. It is unclear exactly how patients were selected for this study and the level of masking of subjects or observers was not stated.

The CPT measurements were significantly elevated in both the feet and hands of the diabetics as compared to the controls at each frequency level ($p<.001$ for each stimulus frequency). Likewise, VPT was significantly increased in the feet and hands of diabetics as compared to controls ($p<.001$). However, for TPT, while the thresholds for both warm and cold were significantly elevated in diabetics on the feet ($p<.01$), there was no difference in TPT threshold (either warm or cold) in the hands. Correlation coefficients were also established. The best correlation was found between CPT at 2000 Hz and VPT ($r=.48$, $p<.001$) in the feet. Internal CPT correlations were weakest for the 2000 Hz and 5 Hz stimuli. Reproducibility was established by testing three diabetics and three controls using CPT, VPT, and TPT at monthly intervals on four occasions. The authors founds that CPT reproducibility was better in the control group than in the diabetics group.

A closer look at the data showed that there were nine diabetic subjects with normal CPT values at the 2000 Hz level but highly abnormal VPT values. Conversely there were 11 diabetic patients with abnormal 2000 Hz CPT values but normal VPT measurements. This raises the question of the neuroselective ability of VPT as well as CPT. In addition there were 7 diabetic subjects with normal 5 Hz CPT values and highly abnormal 2000 Hz values indicating a large fiber dysfunction. In these 7 patients VPT was raised (as expected) but TPT was also elevated for both warm and cold indicating a small myelinated and non-myelinated fiber abnormality that was not detected by the other CPT stimuli; hence CPT may be less sensitive than other QSTs. Finally, reproducibility testing demonstrated that CPT, VPT and TPT had larger coefficients of variation in diabetics as compared to controls, and that the reproducibility of CPT testing decreased as the frequency of stimulus decreased.

Rendell and Bamisedum (1992) investigated the use of pentoxifylline in the treatment of diabetic neuropathy. As part of their evaluation, various tests, including CPT, were performed pre and post-treatment. Thirty diabetic patients with sensory neuropathy between the ages of 18 and 72 were enrolled in the study. Six patients were excluded from data analysis - four because they could not comply with the pentoxifylline regimen and two because psoriasis interfered with interpretation of skin blood flow (one of the tests in addition to CPT used to follow these patients). This left 24 patients for data analysis. Prior to treatment with pentoxifylline all patients had a neurologic examination, laser Doppler skin blood flow measurement, and CPT. Patients were then treated with the drug daily and the aforementioned tests were repeated at three and six months after treatment initiation. At the end of the six months, 17 of the 24 (71%) patients reported subjective improvement in neuropathy symptoms. The physical exam score was significantly improved at six months as compared to baseline in the lower extremities ($p<.01$) but not in the upper extremities. The skin blood flow measurements also showed improvement in the lower extremities at six months ($p<.05$) but not in the upper extremities (no significant change). CPT scores, however showed a sharp drop in both lower and upper extremities at six months ($p<.05$).

There are several significant flaws in this study. First, the patient selection methodology used was unclear. Although there is a detailed list of inclusion/exclusion criteria, the manner by which patients were recruited (e.g., consecutively seen patients) was not stated thus it is not clear that selection bias was minimized. In addition, there was no information on the level of masking of the observer to the study hypothesis or treatment, and there was no control group included in this study.

Rendell, Dovgan, Bergman, et al (1989) investigated the use of CPT in nondiabetic and diabetic subjects (with and without peripheral neuropathy) for the purpose of determining how CPT scores correlated with symptom and physical exam. A detailed clinical neurological exam was performed on 44 nondiabetic (mean age 39±2 years) and 59 diabetic (mean age 44±2 years) subjects. Patients' symptoms and neurological exams were scored using a standardized method. It is unclear from this study if the scoring method had been independently validated. The physical exam included tests for light touch, pain, vibration, and thermal sensation at the hand, wrist, elbow, foot, ankle and knee. CPT measurements were done at each of these sites at the 5, 250 and 2000 Hz frequencies by a technician masked to the results from the clinical assessment. It is not clear from the article's methodology section how patients were recruited for the study or if the inclusion criteria were determined in advance.

The authors stated that they found no effect of age on CPT measurements in the nondiabetic group. They went on to say that this was in agreement with their previous study. Their previous study, Katims et al 1987, was reviewed earlier in this assessment under "Normal Values." As noted in the section on normal values, however, the 1987 Katims et al publication differed from the 1986 Katims et al publication in the effect of age on normal CPT values. In addition, the mean age of the normal subjects (39±2 years) was quite young and, therefore, neither large enough nor sufficiently representative to detect an age effect.

The authors found that symptoms scores and physical scores were associated with an overall correlation of .66. The correlations between CPT and physical scores were .55 at 5 HZ, .60 at 250 Hz, and .62 at 2000 HZ. The CPT and symptoms scores were associated with lower correlation coefficients (e.g., .45 at 5 HZ, .46 at 250 Hz, and .51 at 2000 HZ). CPTs (combining all three frequencies) correlated best with numbness (r=. 5) than with pain (r=. 29) or paresthesia (r=. 24). Vibratory sensation correlated better with CPTs (r=. 61) than did thermal sensation (r=. 54), pinprick (r=. 57) or light touch (r=. 59).

The authors concluded that the overall correlation between the physical exam scores and CPT were strong, despite the fact that the highest *r* value was .62. It is also of note that the correlation of CPT values with symptoms was weak - the best correlation was with numbness at only .5. Finally, the best correlation with a physical test was with vibration perception testing using the biothesiometer. This is a test of large fiber function and can also be tested using standard nerve conduction tests. It should be noted that correlation coefficients are relatively poor measures for determining how diagnostic tests compare to one another.

Rendell, Katims, et al (1989) studied CPT, NCS, and vibration threshold in assessing the quantitative level of correlation with severity of diabetic neuropathy. Seventy-one patients (mean age 54 ± 2 years) with varying severity of diabetic neuropathy were enrolled in the study. All patients underwent a detailed history and physical exam. Sensory and motor nerve conduction studies and CPT measurements (at 5, 250, and 2000 Hz) were performed in the subject's upper and lower extremities. Vibration thresholds were also measured in all patients. In addition, 28 of the 71 subjects had repeated evaluations at 2, 6, 10, and 12 months after the initial procedure. No information was provided on inter-test reliability of CPT values in these 28 patients who were serially tested.

The authors found that correlations of symptoms and physical findings were higher for both vibration threshold and CPT than for NCS. The highest correlations were exhibited between CPT and a composite score of physical findings (based on the NDS) for the lower extremities (for 5 HZ r=. 53, for 250 Hz r=. 57, and for 2000 HZ r=. 53). The NDS used was carried out in a standard fashion as described by Dyck et al.[8]

The authors, however, did not provide information on the diagnostic accuracy of CPT testing, and NCS and vibration threshold were not directly compared to CPT at any stimulus frequency (only correlates were given). Also, the clinical utility of information gathered from CPT testing in these patients was not addressed (i.e., how such information might affect patient management). Finally, it is not clear if the schema the authors used to denote clinical severity had ever been independently validated.

Veves et al (1991) provided the only study that compared morphological findings from sural nerve biopsy specimens from diabetic neuropathic patients with biopsies from non-diabetic, non-neuropathic controls and correlated the findings with electrophysical studies and QST (VPT, TPT, and CPT). Fifteen type I and type II diabetic patients (mean age 47 years, mean duration diabetes 16 years) and eight healthy control subjects (mean age 48 years) were enrolled. Diabetic neuropathy in the 15 patients, demonstrated by abnormal VPT and abnormal peroneal nerve motor conduction velocity, was graded as either stage 1 (present but asymptomatic) or stage 2 (mild symptoms). CPT testing at 5, 250 and 2000 Hz was performed over the great toe and VPT and TPT testing was done over the great toe and medial malleolus. The same individual did all electrophysical tests and it is unclear what the level of masking was. There was no information presented on who performed the QST testing and what level of masking was utilized.

The authors reported that myelinated nerve fiber density was reduced in the diabetics as compared to controls ($p < .01$). There was a strong correlation between nerve fiber density and sural sensory conduction velocity (r=. 84, $p < .001$), sural action potential amplitude (r=. 74, $p < .001$), and peroneal motor conduction velocity (r=. 58, $p < .02$). There was no correlation, however, between myelinated nerve fiber density and any QST (VPT, TPT, or CPT at 5, 250 or 2000 Hz). This study suggests that NCS is superior to CPT in diagnosing neuropathy affecting myelinated nerve fibers.

Veves et al (1994) undertook their study to examine the differences in peripheral and autonomic nerve function in type I or II diabetic patients with varying degrees of diabetic neuropathy. They included four groups in their study: group 1 - 38 diabetics without neuropathy (mean age 50.9 years); group 2 - 32 diabetics with painless neuropathy (mean age 49.2 years); group 3 - 52 diabetics with painful neuropathy (mean age 51.5 years); and, group 4 - 24 healthy subjects with no evidence of diabetes or neuropathy (mean age 47.9 years). The diagnosis of peripheral neuropathy was based on at least two of the following four criteria - clinical symptoms, clinical signs, quantitative sensory testing (abnormal VPT, TPT, or both), and electrophysiology. Patients were randomly recruited from a diabetes clinic and were matched for age. Patients in groups 2 and 3 were also matched for duration of diabetes. All patients were administered the Neuropathy Symptom Score (NSS), the Neuropathy Disability Score (NDS), VPT, TPT, CPT (at 5, 250 and 2000 Hz stimuli), peroneal motor conduction velocity testing, and three autonomic nerve function tests (i.e., orthostatic blood pressure, heart rate change during respiration, immediate heart rate response to standing). CPT testing was done on the right great toe and right index finger. The NSS and NDS measurements used in this study were described by the authors in a previous study.[9]

The authors reported that NSS and NDS were significantly higher in group 3 patients as compared to group 1 and group 2 patients ($p < .0001$ for both comparisons), and in group 2 as compared to group 1 ($p < .05$). VPT was similar in groups 2 and 3, but was higher in both groups as compared to group 1 (no p value given). Similar results were obtained for TPT although the authors did provide data showing that the difference between groups 3 and 2 compared to group 1 was significant ($p < .0001$). There was no difference between the CPT values (all three frequencies) in group 1 (diabetics without neuropathy) and group 4 (healthy controls). This is potentially important because the manufacturer has stated that CPT is able to detect neuropathic changes early in diabetics, before clinical neuropathy develops. There is no evidence that this was achieved in this study.

No difference was found among all four groups in the CPT measurements (all three frequencies) at the index finger. At the great toe there were no differences at the three frequencies between groups 2 and 3. Also, there was no difference in any CPT values between groups 1 and 4. The 5 Hz measurements in group 3 were higher compared to group 1 ($p < .05$). In groups 2 and 3 the 250 Hz and 2000 Hz measurements were significantly different as compared to groups 1 and 4 ($p < .05$).

Correlation coefficients were established between the NSS and the various tests when all diabetics patients (i.e., groups 1, 2, and 3) were considered as one. The correlations values (as compared to NSS) are listed in the table below:

Test	r value	p value
CPT @ 5 Hz	.19	<.05
CPT @ 250 Hz	.19	<.05

Test	r value	p value
CPT @ 2000 Hz	.30	<.001
VPT	.49	<.001
TPT	.23	<. 02

The authors did not provide information as to whether the observers were masked to the patient group when performing the various tests. Also the correlation values listed above are comparing CPT to NSS and not to another QST. Thus one cannot make a conclusion regarding CPT and VPT or TPT based on the above data. The NSS instrument used in this study was previously described by the authors (as mentioned above). However, it is unclear if this is the same NSS measure as described by Dyck et al[10] (and that formed the basis for the modified NSS used by Donaghue et al, 1995) described earlier in this memorandum. As such, the validity of the NSS used by Veves and co-authors is unclear. Nonetheless, based on the findings in the above table, CPT appeared to correlate poorly to the NSS they used in assessing neuropathy in their study patients. The best QST correlation to their NSS was with VPT.

The objective of the study by Vinik et al (1995) was to determine the diagnostic value of various cutaneous sensory tests in diabetic neuropathy. They enrolled 81 diabetic subjects (drawn from patients who were either referred for consultation or recruited as part of other clinical trials of diabetic neuropathy) and 32 controls subjects. All study subjects had the following tests performed: VPT, TPT (warm and cold), SWM test (for touch/pressure), CPT (at 5, 250, and 2000 Hz) and three autonomic function tests (heart rate variability during deep breathing, Valsalva, and postural change). CPT testing was done on the dorsal surface of the dominant hallux. All 81 diabetic patients had symptoms of neuropathy for at least six months and all had signs of symmetrical polyneuropathy (abnormal pinprick, temperature, touch or vibratory sensation by clinical exam). None of the diabetic patients had a foot ulcer. The control subjects had no history of any condition that is associated with neurologic damage although it was not stated if they underwent a confirmatory neurological examination.

A total of 76 of the 81 diabetic subjects underwent all sensory testing. Of these 76 patients, 72 (95%) had an abnormality on at least one sensory test. The VPT was the most frequently abnormal test (88%), followed by warm TPT (78%), and cold TPT (77%). CPT testing at all three frequencies was abnormal in 48% to 56% of patients. The authors also reported on the sensitivity and specificity for the various QSTs. It should be noted that in order to detect sensitivity and specificity, the authors employed signal detection theory and receiver operating characteristic curves were generated. The cut-off level for each modality was calculated by accepting the first standard deviation that achieved a >90% specificity. As such, these values are open to bias from the authors assumption of a >90% specificity. They are useful, however, for comparing between the various QSTs within this study. As the table below shows, using the author's assumptions, CPT testing was associated with much lower sensitivities than the other QSTs.

QST	Sensitivity	specificity
warm TPT	78%	91%
cold TPT	77%	97%
VPT	88%	91%
SWM (touch/pressure)	77%	95%
CPT @ 5 Hz	52%	91%
CPT @ 250Hz	48%	91%
CPT @ 2000 Hz	56%	91%

The authors also calculated kappa statistics for the different tests to assess their reliability[11] (see below):

QST	kappa
warm TPT	.76
cold TPT	.72

QST	kappa
VPT	.83
SWM (touch/pressure)	.66
CPT @ 5 Hz	.68
CPT @ 250Hz	.74
CPT @ 2000 Hz	.63

Using cut-off values of .75-1.00 as demonstrating excellent agreement, .50-.74 as fair/good agreement, and < .50 as poor agreement, the data shows that all sensory tests employed had fair to excellent reliability. VPT was associated with the greatest kappa statistic and CPT at 2000 Hz was associated with the lowest.

There are several important limitations with this study. First, the control patients were younger (mean age 33 $\pm$3.2 years) than the diabetic patients (mean age 53 $\pm$3.6 years), and this difference was statistically significant at the $p < .01$ level. Also the authors did not present information on co-morbidities in either group (e.g., alcohol consumption) nor did they discuss if the observers were masked in the study. Thus it is not clear how comparable the two groups of patients were on characteristics other than presence of diabetes and diabetic neuropathy. Finally, it should be noted that in a letter to the editor of the journal in which this article was published, the president of Neurotron, Ralph Cohen, criticized Vinik and co-authors for analyzing each test frequency separately. However, many other authors have also reported and analyzed CPT data by individual frequency. Indeed, the manufacturer has asserted to CMS on multiple occasions that a unique property of the device is its ability to differentiate the three nerve fiber types by the three test frequencies, and that evaluating the test frequencies separately provides useful information.

Analgesia-related studies involving CPT

Angst et al (2001) undertook their study to investigate the time course and magnitude of analgesia to experimental pain after administration of sustained-release hydromorphone as compared with that after immediate-release hydromorphone or placebo. The CPT device, at the 5 Hz frequency, was used to deliver nociceptive (e.g., pain-eliciting) stimuli to an area of the right upper lateral arm. Twelve healthy subjects (mean age 27 years) participated in the study. They received an initial dose of immediate-release hydromorphone and had their pain threshold measured (PPT and PTT). This was followed by a randomized, double blind series of tests (each done at least five days apart) where they were given sustained-release hydromorphone or placebo. The authors reported that administration of the sustained-release drug was associated with a significant relationship between plasma concentration of drug and measured analgesic effect for maximally tolerated stimulus (PTT) but not for pain threshold (PPT). In general, this study provided more information on the efficacy of sustained-release hydromorphone than on the utility of the CPT device in patient diagnosis and management.

The goal of the study by Liu et al (1995) was to gain insight into the physiology of differential nerve block after lidocaine-induced spinal anesthesia. The function of the different nerve fiber types was quantitatively measured over time and these measurements were correlated with the regression of anesthesia to pinprick, touch and cold. Six volunteers received lidocaine-induced spinal anesthesia at the L2-L3 disc interspace. CPT measurements were done at 5, 250 and 2000 Hz above the medial aspect of the knee. CPT measurements were taken at baseline, 30 minutes after the initiation of anesthesia, and every 10 minutes thereafter until they returned to within 10% of baseline levels. CPT measurements at these three frequencies were also done before anesthesia and 30 minutes after its initiation at the C2 dermatome to verify the lack of a systemic effect from the spinal anesthesia. Dermatomal levels to pinprick (using an 18 gauge needle), touch (self-assessed) and cold (using an ice-cold test tube) were assessed every 10 minutes after initiation of the anesthesia.

The authors reported that C2 level CPT values did not change. The CPT values at the L2-L3 site however did rise dramatically after initiation of anesthesia and returned to normal in the order of touch, then pinprick, and then cold. Return to baseline of the 2000 Hz CPT correlated with the return of sensation of touch (R^2 = .7). Return to baseline of the 250 Hz CPT correlated with the return of sensation of pinprick (R^2 = .75). Return to baseline of the 5 Hz CPT correlated with the return of sensation of cold (R^2 = .67). The authors did not state how return of sensation was converted into data points. Also, although statistically significant differences were reported between the recovery at 250 Hz and 5 Hz, a regression plot of these two frequencies, and their recovery, showed almost complete overlap of the two. Therefore, it is unclear if there is an association between any of the stimulus frequencies and a particular sensory modality.

Park, Wallace and Schulteis (2001) compared thermal perception threshold (TPT) testing, von Frey tactile stimulation, and CPT testing in normal patients who were given a sensory-altering medicine and an active placebo (e.g., diphenhydramine). Nineteen healthy controls (average age 41$\pm$16.9 years) were enrolled in the study. They were administered the following four sensory tests: touch, cold and warm sensation, cold and hot pain, and CPT. All testing was performed on the left forearm. In each patient testing was done both after the intravenous administration of active drug (alfentanil) and active placebo (diphenhydramine). The order of which drug was given first was determined in a random manner. Study sessions (active drug or active placebo) were separated by one week. They hypothesized that the effect of alfentanil would be similar on all the tests.

The authors reported that the TPT showed good repeatability with small ranges around most test means (cool threshold -1.81±13.36%, warm threshold -1.80±17.66%, hot pain 2.41±15.56%) with the exception of cold pain (25.5±315.94%). In addition, the repeatability of "CPT pain threshold" testing was also large (5Hz 21.14±219%, 250 Hz -.21±78.5% 2000 Hz .98±88.32%). According to the authors, "there appeared to be a correlation between the CPT 5 Hz pain threshold and the TST cold pain and warm sensation" tests. The authors, however, did not provide statistical analyses to corroborate this statement. In addition, there was no effect of alfentanil on the von Frey test and the CPT 2000 Hz thresholds. However, the authors noted that they did not see the predicted relation between the 250 Hz CPT stimulus and cool sensation. The authors also looked at the dose-dependency of the sensory tests to alfentanil and noted that while three of the four thermal sensory test thresholds were affected by the drug in a direction consistent with its analgesic effect, only one of the CPT measurements, 5HZ pain threshold, showed a similar dose-response. Finally, the authors noted that all CPT measurements had poor repeatability with confidence intervals that were 4.5 to 17 times higher than those for any of the TST measurements other than cold pain threshold. With perfect repeatability signified by a value of "0" the repeatability measurements for TST were (mean score ± 95% confidence interval): TST cool sensation -1.81±13.36%; warm threshold -1.8 ± 17.66%; cold pain 25.5 ± 315.94%, warm pain 2.41 ± 15.56%. For CPT testing the repeatability measurements were: 5 Hz 5.24 ± 229%, 250 Hz -.21 ± 78.50%, and 2000 Hz .98 ± 88.32%.

Some issues regarding this study needs to be addressed. First, it is unclear to what level (if any) observers were masked to the drug group or stimulus level. Also, the large variability with CPT testing is problematic because it calls into question the reliability and reproducibility of CPT data. Finally, the failure of a correlation between the 250 Hz stimulus and the thermal test raises concerns about the purported fiber selectivity of the CPT test. As stated previously in the Background section, the manufacturers states that the three frequencies (5, 250 and 2000 Hz) correspond directly to the three different nerve fiber types, C, A-delta, and A-beta, respectively.

Radwan, Saito, and Goto (2001) examined the effect of peripheral nerve block with high concentration tetracaine, an anesthetic, for the management of trigeminal neuralgia and they examined the sensory function by measuring postblock CPT values. This case series involved five elderly subjects (mean age 74.8 years) with a history of second division trigeminal neuralgia. The five subjects received an infraorbital nerve block using high concentration tetracaine. The reported analgesic effect in all patients was immediate and lasted a median of two months. Sometime after the onset of analgesia the subjects had their blocked and healthy infraorbital areas tested using CPT at 5, 250 and 2000 Hz stimuli. They also had cold sensation measures taken around the block sites.

In no patient were the CPT measurements significantly different between the blocked and control sides, indicating that, despite adequate infraorbital nerve analgesia, the tetracaine block did not dampen the patients' infraorbital sensation as determined by CPT. Although they stated that cold testing was done on the patients, no data for this was presented. Thus, there was no comparison information for CPT versus another modality.

Tay, Wallace and Irving (1997) investigated the effect of epidural anesthesia in seven patients with lower extremity pain and one patient with lower abdominal pain using CPT as well as pinprick, touch and cold sensation as determined by physical exam. Their study design was single masked, placebo controlled. Each patient had an epidural cannula placed at the L3-L4 disc interspace. Saline was administered first as the placebo, and this was followed by administration of 2% lidocaine. CPT measurements (at 5, 250, and 2000 Hz) were taken at the mastoid, umbilicus, knee, and great toe prior to the lidocaine administration. After lidocaine was given, CPT measurements, along with touch, pinprick and cold sensation, were done at these same sights. Tests were done at 15, 45, 75, 105, and 135 minutes after lidocaine infusion. In addition, a visual analog scale was used to assess the patient's pain level before epidural placement, after saline administration, and 15 and 45 minutes after the lidocaine was given.

The authors found that saline had no effect on the CPT values at any tested frequency or site (mastoid, umbilicus, knee, or great toe). After the administration of lidocaine, CPT values at the mastoid also did not change. Lidocaine, however, did increase the CPT measurements at all frequencies at the umbilicus and knee. This increase, however, only reached statistical significance at 5 Hz for the umbilicus test site ($p < .05$). The great toe showed a slight increase in 5 Hz CPT values although this was not statistically significant. There was no change in CPT values at 250 Hz or 2000 Hz at the great toe.

The results of touch, pinprick and cold testing showed no effect of saline on their values nor did these test values change with administration of lidocaine at the mastoid level. Administration of lidocaine did cause a significant decrease in all these measurements at the umbilicus and knee ($p < .05$). At the great toe, however, only cold sensation was significantly decreased after lidocaine was given ($p < .05$). While there was a modest (not statistically significant) decline in pain score after the administration of saline, there was a significant reduction in the pain score at both 15 minutes and 45 minutes following lidocaine ($p < .05$).

This is a small case series, and there is no indication that observers were masked. What is also interesting is that touch, pinprick and cold sensation were more broadly changed following lidocaine administration than CPT. This calls into question the issue of selectivity of CPT for nerve fiber type, and how this nerve fiber selectivity is manifest on different QST. It is unclear why post-lidocaine CPT only significantly differed from pre-lidocaine values at the umbilicus at 5 Hz while the other QSTs had a wider range of significant change. A study with proper masking and control groups, and a statistical comparison of CPT to the best reference test, would have been more helpful to demonstrate that CPT can assess analgesia post-epidural anesthesia. However, this study suggests that CPT is no more accurate than a physical exam.

Neuropathy associated with dialysis

Avram (1993) presented a paper at a National Institutes of Health Consensus Development Conference in November 1993. The author stated that he and his colleagues (names and affiliations not listed) routinely performed CPT in their dialysis patients since 1991. CPT measurements were performed over the peroneal, median and ulnar nerve distributions at 5, 250, and 2000 Hz. The author stated severe neuropathy was defined as an anesthetic response to any one of the three frequencies. Evidence supporting this definition of “severe” neuropathy was not given.

Avram provided data on 95 dialysis patients - 60 non-diabetics and 35 diabetics. According to the author, 63% of diabetics demonstrated severe neuropathy as compared to 32% of non-diabetics and this difference was significant at the p=.003 level. He also reported that severe neuropathy was highly predictive of 1-year mortality in non-diabetics on dialysis but not in diabetics on dialysis. However, the author left many questions unanswered. There was no information on exactly how patients were selected for this study, and there was no information on confirmative physical exam findings (e.g., was the presence of neuropathy confirmed by physical exam and did CPT provide better diagnostic information than physical exam or was physical exam adequate to diagnose the presence of "severe" neuropathy). Indeed, Avram based the diagnosis of severe neuropathy on CPT findings - the test in question. Also, the CPT testing in this study involved a single blind method, but the current recommendations from the manufacturer are to use the device in a double-blind testing method.

Katims, Taylor and Weseley (1991) investigated the peripheral and central sensory nervous system in 19 patients on chronic hemodialysis. The peripheral nervous system was assessed using the CPT test at 5, 250 and 2000 Hz and tested over the distribution of the median and ulnar nerves bilaterally in each patient. The central sensory nervous system was assessed using a different technique - cephalic evoked non-cutaneous testing. For the purposes of this decision memorandum CMS focused on the CPT results. The CPT results in these 19 patients were compared to previously tested, healthy subjects. The authors provided no more information on these healthy subjects and it is unclear what normative data was used. The mean age of the patients enrolled was 47 years (range 17-77) and the median duration of dialysis was 3 years (range 1-14). The underlying cause for the patient's renal failure was not stated and the authors did not discuss how underlying disease states could have contributed by themselves to the development of neuropathy. CPT abnormalities were noted in 32% of patients.

The CPT testing procedure used was a single-blind method where only the subjects were unaware of the stimulus being delivered. In addition, the authors did not provide any information on patient selection criteria and there was no comparative diagnostic test used to assess peripheral nervous function in these subjects. The authors concluded that CPT provides a sensitive and easy test for the purpose of assessing the adequacy of dialysis in these patients. However, we cannot be confident in this assertion due to the methodological problems noted above, especially the lack of a comparative assessment.

Weseley, Liebowitz, and Katims (1989) reported on the ability of CPT and standard NCS to detect peripheral nerve dysfunction in patients on dialysis. They studied 34 patients on either hemo- or peritoneal- dialysis. Patients underwent bilateral motor median and peroneal NCS. CPT testing (at 5, 250 and 2000 Hz) was done over the distribution of the median and peroneal nerves. CPT testing was done concurrently with a dialysis session. It was not stated when in relation to dialysis NCS studies were done. No confirmatory neurological evaluations were noted. The authors reported that in detecting median and peroneal neuropathy, NCS was associated with sensitivities of 32% and 65% respectively while CPT was associated with sensitivities of 44% and 71% respectively. No specificity data was reported nor was it clear against what reference standard NCS and CPT were compared when deriving these sensitivity values. As stated earlier, we cannot draw conclusions about the accuracy of a diagnostic test without both sensitivity and specificity data. In addition, the method by which patients were selected and included in the study was not stated nor was there any indication that observers were masked.

Wesley et al (1988) examined 23 patients on hemodialysis using CPT and NCS. This was a one-year longitudinal study in which CPT and NCS measurements were performed at the beginning of the study period and again one year later. CPT measurements were done on all patients while they received hemodialysis and readings were taken over the median and peroneal nerve distributions at 5, 250 and 2000 Hz frequencies. NCS measurements were also performed in the median and peroneal nerve areas although the article did not state if NCS was done the same day as CPT testing or if NCS was also done during dialysis. In addition, it was not stated if the observers were masked to the results of either testing modality nor were the patient selection procedures/criteria defined. The authors stated that normative data from previous studies were used for comparison. These normative data came from the Katims et al 1987 study reviewed earlier. CMS has concerns with relying on normative data from one study group, especially given that this study group's normative data was not obtained in a manner that would provide truly representative population information.

Wesley and co-authors reported that CPT and NCS tests (at both median and peroneal nerve sites) were associated with a correlation coefficient for the initial test of .83 and .8 for the one-year follow-up. In addition, they reported that the combined (median and peroneal nerve) sensitivity for CPT on initial testing was 76% as compared to 65% for NCS. At the one-year follow-up the combined, reported sensitivity was 87% for CPT and 78% for NCS. No specificity data were given. It is unclear to what reference standard CPT and NCS testing were compared when calculating the sensitivity data. The authors stated that each subject possessed neuropathy, but there was no mention of how that was determined. Second, no data was presented on the number of test positive and test negative cases for either CPT or NCS.

Carpal tunnel syndrome

Franzblau et al (1994) investigated the use of CPT in screening workers for carpal tunnel syndrome (CTS). Eighty -four workers in an automobile plant who regularly engaged in repetitive-type work movements of their wrists participated in the study. All subjects completed a symptom-survey, had electrodiagnostic testing of their median nerve and had CPT testing of their second finger (i.e., median nerve distribution). Diagnosis of CTS was made if a subject had both a median mononeuropathy on electrodiagnostic testing and symptoms consistent with CTS. Of the 83 subjects who completed CPT testing, 35 had abnormal CPT readings on their 2nd digit. A median nerve mononeuropathy was noted on electrodiagnostic testing in 15 subjects and symptoms consistent with CTS were noted in 17 subjects. A total of seven subjects had both a median mononeuropathy on electrodiagnostic testing and symptoms of CTS. The authors concluded that CPT testing of the 2nd digit for the diagnosis of CTS (reference standard was a combination of electrodiagnostic testing and symptomotology) was associated with the following accuracy values: sensitivity = 53%; specificity = 60%; positive predictive value = 23%; and, negative predictive value = 91%. Predictive values were calculated using an assumed disease prevalence of 15%. The authors concluded that, based upon these results, CPT testing could not be recommended as a screening procedure for the identification of possible cases of CTS among active industrial workers.

This decision memorandum will not address s-NCT as a screening tool since screening tests are excluded by statute unless Congress specifically mandates otherwise, but rather will address its value as a diagnostic test. In addition, the utility of a screening test is affected by a disease's prevalence, and the prevalence in this study was assumed. Nonetheless, the sensitivity and specificity of any test is independent of the disease prevalence and the low validity values for CPT noted in this study are concerning, especially given that the manufacturer has told CMS that the device can be used to diagnose CTS.

It should be noted that Dr. Katims (one of the inventors of the Neurometer®, an investigator of this technology, and Director of Research for the company that produces the Neurometer®) wrote a letter to the editor of the journal in which the Franzblau et al article appeared[12]. Dr. Katims criticized the authors for not following the Manufacturer's Recommended Guidelines, for selectively analyzing only portions of the CPT data, thus missing underlying associations between CPT results and clinical outcomes, and for ignoring the "U-shaped" distribution of CPT values which allow for the separation of responses into "hypoesthetic", "normal", and "hyperesthetic". The authors' reply addressed Dr. Katims criticisms. They stated, as indicated in the article, the physician who administered the CPT tests had completed the usual certification course offered by the manufacturer in which most of the training was conducted by Dr. Katims himself. The authors also stated that all CPT testing was conducted using the manufacturer's recommendations, all raw CPT data were fully analyzed by the software provided by the manufacturer, and all parameters generated by the CPT software were employed in their analyses. In response to the criticism that only selected portions of the data were analyzed, Franzblau and co-authors stated that all data generated in the CPT testing from all frequencies was analyzed and no parameters were excluded from analysis[13]. Finally, in regards to the "U-shaped" profile of CPT results, the authors stated that their study was not designed to test whether CPT can discern such differences in nerve function (e.g., hypoesthetic or hyperesthetic). They went on to state that having reviewed the available literature, they believe there is no foundation for such distinctions using CPT and that there is no data to support the notion that hyperesthesia as determined by CPT testing is an early manifestation of nerve damage or that such patients will progress to hypoesthesia.

Katims et al (1989) investigated the ability of CPT to diagnose carpal tunnel syndrome (CTS) in patients receiving hemodialysis. Twenty-nine patients who were stable on hemodialysis completed a questionnaire to identify symptoms of CTS. CPT was then performed on these patients at three sites (median, ulnar, and peroneal nerves) at the three standard CPT frequencies (5, 250, and 2000 Hz). Standard nerve conduction studies (NCS) were done on all patients at the median and peroneal nerves. Patients suspected of having CTS had further NCS of the hand including the ulnar nerve. The authors did not state how the suspicion of CTS was established (i.e., if based on initial NCS readings or other criteria). The authors also reported that the sensitivity for detecting CTS was 92% for CPT and 79% for nerve conduction studies. It is unclear from the article what the reference standard was to which both CPT and NCS were compared. In addition, there was no information on how the patients were selected for this study nor was there information on the masking of the investigators to the questionnaire results or the results of either study.

Katims, Patil et al (1991) investigated the diagnostic ability of CPT in testing for CTS in symptomatic workers. The study was conducted at a food processing plant where workers who self-reported to the occupational medicine clinic with hand pain were invited to take part in the study. Patients with a history of neuropathy of any etiology, had prior hand surgery, were currently taking a narcotic analgesic, did not have symptoms restricted to the median nerve distribution area, or did not have symptoms that occurred away from work were excluded from the study. Twenty-six patients made up the initial pool of subjects and 10 were excluded for at least one of the above reasons. An upper extremity physical exam was performed on the remaining 16 patients. The CPT test was performed in a single-blind fashion on the patient's 2nd digit (e.g., median nerve distribution) at the 5, 250 and 2000 Hz levels. The authors used previously established normative data and compensated for the effects of age on CPT values.

The authors stated that CPT detected abnormalities in 75% of the patients as compared to clinical exam, which detected abnormalities in only 50% of the patients (difference significant at $p<0.05$). They concluded that CPT testing was a sensitive method for detecting CTS in symptomatic patients. A few issues concerning this study and its results must be addressed. First, the CPT method used was a single-blind method, different from the method of double blind testing the manufacturer currently promotes. Having a person administering the test that knows what stimulus is being given to the patient is open to investigator bias. Second, it is unclear what the reference standard was to which CPT was compared. If the authors are using clinical exam and CTS symptomotology as the standard then the following diagnostic test accuracy 2x2 table could be generated from this study:

	Exam and questionnaire +	**Exam and questionnaire -**	
CPT +	5		7
CPT -	3		1

Using this table, CMS calculated a sensitivity of 62.5% and a specificity of 12.5% for CPT testing. The authors concluded that CPT provided a sensitive technique for obtaining quantitative measures in CTS but did not provide an actual sensitivity. It should also be noted that the normative data used in this study came from studies previously reviewed herein (Katims et al, 1986 and Katims et al, 1989). The authors of this study make a point that age affects the normal CPT values and they compensated for this age effect. However, as noted earlier, another study by this same group of researchers (Katims et al 1987) failed to find an age effect for CPT measurement at the toe or finger and only found an age effect for CPT measurements taken on the face.

Hand-arm vibration syndrome

Kurozawa and Nasu (2001) undertook their study in order to evaluate CPT for the assessment of vibration-induced neuropathy. Fifty-nine males with hand-arm vibration syndrome (HAVS) and 20 male control subjects were enrolled. The 59 patients with HAVS were further classified into Stage 1, 2, or 3 HAVS according to a known classification system. All subjects had CPT at 5, 250, and 2000 Hz performed on their index (median nerve) and little (ulnar nerve) fingers. According to the authors, the index finger CPT values at 2000 Hz were significantly elevated in Stage 1, 2 and 3 HAVS as compared to controls. In the figure in the paper that detailed the CPT values at 2000 Hz, however, the p value difference was listed as <. 5. It is unclear if this was a typographical error and was meant to be <. 05. Also, the range of values at 2000 Hz showed considerable overlap between the controls and stage 1, and between stages 1, 2, and 3. The authors also stated that in the index finger at 250 Hz there was significant difference (again with the p value reported as <. 5) between stage 1 and 3 but not between the controls and stage 1. For the ulnar nerve a significant difference (again at a reported p of < .5) was noted at 2000 Hz between controls and Stage 1, 2 and 3. These differences were also associated with considerable overlap on the bar plots. This is important because large overlaps of values, even if the difference is reported to be statistically significant, calls into question the confidence one can place in such reported differences. In neither nerve distribution were the CPT results reported as significantly different at 5 Hz between the HAVS and control subjects.

As with many of the other studies reviewed, Kurozawa and Nasu did not provide information on exactly how patients were recruited for the study (e.g., were they consecutive patients with HAVS seen during a certain time period at their hospital, how many were invited to enroll, did any decline, what were the inclusion/exclusion criteria). The authors did not state how patients were diagnosed with HAVS, and it was not clear if the person who administered the CPT test was masked as to the study hypothesis or patient diagnosis. Finally, this study does not permit the calculation of sensitivity and specificity for CPT in the diagnosis of HAVS and it does not provide information on how the values obtained could guide patient treatment or management.

Pelmear and Kusiak (1994) evaluated 364 men with occupational exposure to hand-arm vibration with history, physical exam, vascular tests, and neurological tests including depth sense aesthesiometry, two-point discrimination, grip strength, vibrotactile test, motor and sensory NCS, and CPT evaluations. After excluding patients with defined co-morbidities or those who also had non-occupational hand-arm vibration exposure, 173 men were left for analysis. The authors used a statistical clustering algorithm to categorize 138 male subjects according to the results of their diagnostic tests.[14] Because CPT testing was not introduced until 1990, the patients who had CPT testing, as well as the other sensory and vascular tests, were excluded from the cluster analysis accounting for only 138 (not 173) subjects in the cluster. The authors reported that sensory clusters tended to correlate with the 2000 and 250 Hz stimuli in the ulnar and median nerves, but there was only weak correlation to the 5 Hz stimulus. Interestingly, the 250 Hz stimulus was reported to correlate well with vibration threshold. This is surprising since, if the CPT stimuli are truly selective for nerve fiber type, one would not expect the 250 Hz frequency, which is associated with small, myelinated fibers, to correlate with a sensory test that is generally associated with large, myelinated fibers. In addition, there were no statistical analyses given to demonstrate the correlations the authors described. Finally, it would have been helpful to have the CPT values compared directly to the NCS results; however, this was not provided.

Intervertebral disc disease

BenEliyahu et al (2000) performed CPT and MRI on 70 consecutive patients with clinical signs and symptoms of intervertebral disc syndrome. Two patients had both cervical and lumbar evaluations, which should have yielded a total of 72 CPT/MRI evaluations. The data presented, however, demonstrated only 69 evaluations. The reason for this discrepancy was not addressed. The authors reported that 50/70 patients had both a positive MRI and CPT and that 42 were level specific. They noted that this yielded a sensitivity of 84% for CPT testing.

It is difficult to follow the numbers in this study that lead to the calculation of the accuracy values. It appears that this study's purpose was to compare CPT diagnostic ability to MRI in patients with signs and symptoms of disc disease. The authors presented the following table of findings:

Findings	N

Findings	N
- MRI/ - CPT	2 (3%)
- MRI/ + CPT	12 (17%)
+ MRI/ - CPT	5 (7%)
+ MRI/ + CPT	50 (72%)

Using these numbers, and rearranging into a typical epidemiologic 2x2 table, yields the following:

	MRI +	MRI
CPT +	50	12
CPT -	5	2

From this table, one can calculate the sensitivity as [(50/(50+5)x100%] 91%, and specificity as [(2/(12+2)x100%] 17%. This sensitivity of 91% differs from the reported value of 84%. In addition, the calculated specificity is very low and reflects the high number of false positive results seen with CPT in this study. If MRI is the test the authors considered the most appropriate reference standard diagnostic test in these patients, then to demonstrate that using CPT provides value to patients, the study would have to find one of the following: 1) CPT provides diagnostic information as (or more) accurate than MRI, or 2) CPT provides information that affects patient management more positively than MRI. The article did not support the former (i.e., that CPT is at least as accurate as MRI) and did not address the latter.

Yamashita et al (2002) evaluated the severity of sensory disturbances quantitatively in patients with lumbar radiculopathy. The study included 48 patients with lumbar radiculopathy secondary to disc herniation and 11 healthy control subjects. CPT testing at 5, 250 and 2000 Hz was done in all subjects on the dorsal side of the first (L5) and fifth (S1) metatarsus in both lower extremities. Pain was scored using a visual analog scale. All 48-disc herniation patients had pain distribution from the compression of one lumbar nerve root (L5 or S1). MRI showed unilateral disc herniation of the corresponding level in all patients.

In the control group there was no significant difference in CPT values at any frequency when comparing the two lower extremities. In the 48 patients with radiculopathy, the affected leg, as compared to the contralateral leg, demonstrated significantly elevated CPT values at each frequency ($p < .01$ at each frequency). When comparing CPT results to the pain scores, there was no significant difference at the 2000 and 250 Hz levels, while at the 5 Hz level CPT values were significantly elevated in patients with pain scores in the severe level ($p<0.05$)

As with many other studies reviewed, there was no detailed description of patient selection methodology nor was there any indication that the observers were masked to the patient group, MRI, or clinical diagnosis. Also there was no comparison of the radiculopathy patients to the control patients. The authors did report that the difference in the affected and unaffected legs were significantly different in the radiculopathy patients; however, a review of the actual CPT values showed that at each frequency there was a large overlap in the confidence intervals. Finally, there was no evidence that CPT was able to provide an accurate assessment of the level of the disc herniation.

Miscellaneous

Husin et al (1999) undertook their study to determine if CPT measurements could be used as a surrogate marker for organophosphate pesticide exposure amongst a group of Malaysian farm workers. They studied 60 Malaysian paddy workers (mean age 45 years, range 28-72) and 19 control subjects (mean age 34 years, range 22-50). Control workers were drawn from the local agricultural office and had no history of pesticide exposure. All subjects had CPT measurements of their median and peroneal nerves performed at 5, 250 and 2000 HZ as well as cholinesterase (ChE) levels measured. Malaysia does not have established normal ChE levels so the authors took 3500 Units as their lower limit of normal[15]. They found that 25% of farmers were classified as having low ChE activity levels. It is unclear from this study what the level of abnormally low ChE activity was in the controls. They stated that 84% of controls had ChE values between 4500 and 6250 Units, but not how many had levels below 3500 Units. The authors found that for the median nerve the CPT values were significantly different among the farmers as compared to the control group at all frequencies: 5 Hz $p<.05$; 250 Hz $p=.012$; and, 2000 Hz $p=.0001$. For the peroneal nerve, however, only the 2000 Hz CPT measurements were significantly different when compared to the controls ($p=.0001$).

This study has several methodological problems. First, the farmers and the controls were not matched for any characteristics. The authors said it was impossible to match them for age because of mandatory retirement ages for office workers in Malaysia, but there was no attempt to match them for exposure to other toxins or metabolic disease which can cause peripheral neuropathies, especially diabetes. Also, six farmers and three control subjects were excluded "due to diseases." The authors did not discuss this further. Thus, there are serious questions about the comparability of the two groups in this study. Second, one observer performed the measurements in both groups and it is not stated if this observer was masked. Also, the authors reported how many farmers had ChE level below their 3500 Unit cut-off but only reported how many controls had ChE units above 4500 Units (84%). Finally, the CPT values showed a pattern that is unique at best and should have been discussed in more detail by the authors. According to their results, the farmers had CPT measurements that demonstrated a neuropathy affecting all three fiber types in the upper extremity but only the largest fiber type in the lower extremity. CMS is unaware of a polyneuropathy from any cause that produces this distribution of nerve fiber involvement, including a toxic neuropathy from organophosphate which tends to produce a sensorimotor polyneuropathy (involvement of sensory and motor nerves that tend to start on the feet, spread up the legs, and then into the hands). The one exception for toxic neuropathies is lead poisoning, which can affect the arms more than the legs, but is primarily a motor neuropathy with generally mild sensory nerve involvement and the pattern is of multiple individual nerves affected (i.e., mononeuritis multiplex) rather than a symmetric polyneuropathy.

Menkes et al (2000) investigated the ability of CPT to diagnose demyelinating polyneuropathies and axonal polyneuropathies. As the authors stated, demyelinating polyneuropathies tend to affect the larger myelinated nerve fibers while axonal polyneuropathies affect the smaller fibers in a distal to proximal gradient. Demyelinating neuropathies are generally diagnosed using NCS and needle electromyography (EMG). Menkes and co-authors prospectively enrolled 10 patients with demyelinating and 10 patients with axonal polyneuropathies. Patients were classified with demyelinating neuropathy based on the presence of at least two of three criteria - reflex or motor power reduction with preserved muscle bulk and tone in an asymmetric or proximal greater than distal distribution, abnormalities on cerebrospinal fluid exam, and a proximal nerve conduction block. Patients were classified as having axonal polyneuropathy based on typical sensory and motor signs in a distal to proximal gradient in addition to other electrodiagnostic criteria.

A technician, masked to the study hypothesis and the patient's diagnosis, performed CPT at the three standard frequencies at sites over the mastoid area, lateral antebrachial cutaneous nerve, and the sural nerve. The authors reported that CPT for the diagnosis of demyelinating polyneuropathies was associated with a sensitivity of 50% and a specificity of 100% while the sensitivity for diagnosing axonal polyneuropathies was 70% (no specificity data for axonal neuropathies were noted).

Menkes and co-authors concluded that CPT should be considered as an adjunctive test to NCS and EMG in the electrodiagnosis of demyelinating polyneuropathies. They did not state what role CPT might have in the diagnosis of axonal polyneuropathies. Since demyelinating neuropathies tend to affect larger fibers first, their diagnosis is already amenable to NCS/EMG studies and it is unclear what additional information CPT provides that would affect patient management (such as increasing the diagnostic yield of NCS/EMG). The article leaves open the question of how CPT fits into the diagnostic armamentarium for axonal neuropathies.

Mironer and Somerville (2000) examined the use of CPT, pain tolerance threshold testing (PTT) and pain perception threshold testing (PPT) to predict spinal cord stimulator (SCS) trial outcomes. The authors described selecting a convenience sample of 44 patients considered good candidates for a SCS and nine healthy volunteers. While the authors did not describe what was meant by a "convenience sample," it is often used in association with a sample not drawn from strict selection criteria. Indeed, the authors did not describe their patient selection methodology in detail. It was unclear from the article at what body sites and what stimulus frequencies the CPT, PTT and PPT tests were conducted. Immediately before the SCS trial procedure, patients underwent CPT, PTT or PPT testing. Initially the type of test performed (CPT, PTT or PPT) was chosen in a random fashion for each patient; however, after the first 20 patients the authors decided to continue investigating only the PTT test. The authors stated that high intra-individual variability with PPT testing was the reason that the PPT test was abandoned. The reason CPT testing was ceased is unclear. Following the initial test, the SCS trial was performed, patients returned 3-5 days later for removal of the SCS lead, and they were retested with the originally selected test. The authors stated that a non-interested party, masked to the outcome of the trial, performed all testing.

The intra-individual variability of PPT testing in the nine control subjects was 46% and the authors felt this was large enough that PPT testing was not reliable in this trial. The intra-rater variability of PTT in the controls was 18% and the authors felt this was of an acceptable level. The intra-individual variability for CPT testing was not stated. In the SCS trial patients, the authors found that CPT measurements did not change significantly after SCS use, but the PTT values did show significant changes ($p<.05$). The authors concluded that CPT changes after SCS were insignificant, and, that although PTT testing did show promising results they felt it was premature to select PTT as an objective criterion for SCS patient selection.

There were several limitations to this study. The method of patient selection was unclear and the selection of a "convenience sample" (as discussed earlier) raises the possibility of selection bias. Also, the authors did not control for confounding factors such as concurrent medial and psychiatric co-morbidities.

Oishi et al (2002) undertook a study to determine if CPT as measured at 5 HZ correlated with sympathetic skin response (SSR) in patients with diabetic and alcoholic neuropathy. Their study included 14 patients with diabetic neuropathy, 10 patients with alcoholic neuropathy and 24 age-matched healthy controls. Their criteria for establishing the diagnosis of diabetic or alcoholic neuropathy were described, and were based on examination. Patients with additional neurologic diseases were excluded. All diabetic and alcoholic patients were drawn in a consecutive manner from their neurology clinic. The manner in which the controls were recruited was not stated. The authors stated that the mean age in the diabetics was 51 ± 6 years, in the alcoholics was 53 ± 7 years, and in the controls was 52 ± 6 years. There was no detailed patient demographic data presented to fully demonstrate the comparability between the groups.

All subjects had CPT measurements performed (5, 250 and 2000 Hz) over the median and sural nerve distribution areas bilaterally. SSR measurements were performed using a device (Neuropack Σ) that measures the amplitude and latency of the median and sural nerve response to electrical stimulation. The authors noted that the CPT 5 Hz and 2000 Hz response were higher in the diabetic and alcoholic group than in the controls, although no significance data were given. They did not discuss the difference between the patient and control groups at the 250 Hz stimulus, but a review of the numbers they provided appeared similar. The amplitude of the SSR, they noted, was smaller in the patient groups than in the controls, however, no significance data were provided. The authors went on to state that the CPT 5 Hz values and the SSR results correlated (p<. 01) in all patients with neuropathy groups. However, they did not do a comparison between diabetic CPT/SSR results and alcoholic CPT/SSR results. They concluded that in diabetic and alcoholic neuropathy CPT at 5 Hz and SSR are impaired. However, the authors also noted that there was no significant correlation between CPT and the clinical symptoms or between SSR and clinical symptoms (the authors did not define how clinical symptoms were measured and quantified).

Raj et al (2001) evaluated CPT and PTT in patients with chronic regional pain syndrome (CRPS).[16] Both CPT and PTT testing were done using CPT at 5, 250 and 2000 Hz in 36 subjects with CRPS and 57 controls. CRPS was diagnosed in each patient using criteria adapted from Stanton Hicks et al.[17] The authors stated that all controls were healthy with no history of neurologic disease, however, the authors did not document that a neurological examination was performed on these controls. The CRPS subjects had their CPT and PTT tested in the symptomatic extremity either on the ring finger or great toe (if the affected extremity was the arm or leg respectively). The same subject also had their ipsilateral ring finger or toe tested for an intra-individual control. The 57 control subjects had their right ring finger and right great toe tested. The healthy controls tended to be younger than the CRPS patients (38 years versus 45 years); there was no information as to whether this difference was significant. The authors stated that CPT values for either CPT or PTT were considered abnormal if they were less than the 5th percentile or above the 95th percentile for the values obtained in the 57 controls.

The authors noted that the highest detection sensitivity of the PTT test was 71% when the toe was the symptomatic site and was tested at the 2000 Hz frequency, and 63% when the finger was the symptomatic site and was tested at the 5 Hz frequency. The highest CPT detection sensitivity was 53% when the toe was the symptomatic site and was tested at the 2000 Hz frequency, and 37% when the finger was the symptomatic site and tested at the 5 HZ level. These are relatively low sensitivity values. The authors noted a significant correlation between the presence of allodynia[18] and the presence of an abnormal CPT or PTT (p< .01). The correlation coefficient was lower for CPT than for PTT (.34 versus .6 for the finger and .48 versus .67 for the toe, respectively).

The method of patient selection Raj and co-authors used was not fully defined. In addition, there is no indication that those involved in measuring CPT and PTT were masked as to the patient group studied. Also, the normal values used against which the CRPS patients were compared were drawn from the 57 control subjects. It is unclear if these 57 patients were truly population-representative. Additionally, the authors did not address why the 2000 Hz stimulus was most sensitive on the toe sites and the 5 Hz stimulus most sensitive on the ring finger. Finally, there was no specificity data presented. Therefore, this study demonstrates that CPT and PTT testing is not a highly sensitive test in detecting CRPS and appears to be less accurate than history and physical in diagnosing this condition.

Ro et al (1999) sought to determine whether CT measurements can be used to assess subjective complaints of pain and paresthesia in patients with Fabry's disease[19] and to correlate NCS findings, CPT results, and biochemical studies with clinical manifestations of the disease. Sixteen patients with Fabry's disease (all from the same family) were included in the study along with 50 healthy subjects. All 16 patients reported pain and received a symptomatic score based on a self-report. CPT measurements were done at 5, 250 and 2000 Hz in the median and peroneal nerve distributions. The location of where the NCSs were performed was not stated.

The authors reported that CPT values were abnormal in 37.5% of Fabry's patients at the 5 Hz level, in 50% of Fabry's patients at the 250 Hz level and in none of the Fabry's patients at the 2000 Hz level. Meanwhile, the NCS results were within the normal range in all the patients with Fabry's disease. The authors also stated that there was no correlation between CPT values and clinical symptom scores, duration of disease, creatinine clearance, or alpha-galactosidase A enzyme levels (the enzyme that is abnormal in Fabry's disease).

This study, however, leaves some questions unanswered. First, it is not clear that patients had a neurological examination to assess their peripheral sensory state. The authors did state that burning paresthesias were self-reported as occurring almost daily in the eight men and intermittently in eight women in the study, however, how this correlated to physical exam findings was not stated. Given that burning-type neuropathies are so common in Fabry's disease patients the utility of CPT in diagnosing such symptoms is unclear. Second, the authors did not calculate sensitivity and specificity data for CPT but only provided the number of CPT tests that were abnormal at each stimulus frequency (these percentages ranged from 37.5 to 50%). It, therefore, appears that CPT was normal in a number of Fabry's patients at the 5 and 250 Hz level. This is problematic since burning paresthesias are thought to be related to the small, unmyelinated C fibers that, according to the manufacturer, are assessed by the 5 Hz CPT stimulus. Third, it is unclear if the person(s) performing the CPT and NCS tests were masked to the patients' diagnosis. Fourth, it is not clear that NCS is an appropriate test against which to compare CPT for the diagnosis of Fabry's disease because NCS generally assesses myelinated fibers that typically are not affected by this disease. Fifth, it is not clear if the normative data to which the patients with Fabry's disease were compared was that data obtained from the 50 healthy volunteers in this study or from the machine's internal normative data. This is very important given the need to have normal data from a representative reference population.

Sensory-Nerve Conduction Threshold Testing using the Voltage-Nerve Conduction Threshold (v-NCT) Test

Two articles were identified that discussed v-NCT (Cork et al, 2002 and Saleemi et al, 2002). Cork et al investigated the sensitivity, specificity and positive predictive value of v-NCT and physical examination when compared to epidurogram. In this study, 49 patients with L5-S1 radicular back pain that were scheduled to undergo lysis for epidural adhesions underwent a pre-procedure v-NCT and physical examination. Using epidurogram as the reference standard, the authors reported that the sensitivity, specificity and positive predictive value for v-NCT was 95%, 70% and 91%, respectively, while for physical examination it was 62%, 72%, and 88%. The authors did not state the criteria used to select their patients (e.g., were they consecutively seen patients) and it was unclear if the observers were masked.

Saleemi et al retrospectively reviewed 50 patients with piriformis syndrome[20] who had botulinum toxin A treatment. Part of the diagnostic work-up on at least 48 of their patients included v-NCT. The authors stated that L5 abnormalities were seen in 7/48 (15%) patients using v-NCT, S1 abnormalities in 9/48 (19%) patients, and both L5-S1 abnormalities in 32/48 (67%) patients. v-NCT was not directly compared to another diagnostic modality and there was no information on how the information obtained via v-NCT affected patient management. The authors did not state why two patients did not receive v-NCT.

Finally, there was no information available on normal values for v-NCT in healthy subjects of varying ages and genders.

Technology Assessment and Position Statement from the American Association of Electrodiagnostic Medicine (AAEM)

The AAEM published a technology assessment of the Neurometer® Current Perception Threshold. This technology assessment also serves as the official position of the AAEM regarding this device. This assessment reviewed many of the same articles CMS reviewed herein. The AAEM concluded that, "CPT has the potential for evaluation of patients with peripheral nervous system diseases resulting in altered cutaneous sensation. This type of testing could potentially complement needle EMGs and NCSs…however, conflicting information and methodologic problems exist regarding the utility of the Neurometer® CPT for the diagnostic evaluation of specific disease conditions such as CTS and polyneuropathy."[21] The AAEM specifically noted the following: 1) reference values need to be established for well characterized and representative populations, 2) the reproducibility and inter-operator variability needs to be better established, 3) sensitivity and specificity need to be established and compared to an appropriate standard, and 4) studies are needed to analyze the cost and outcome when CPT is used for evaluating treatment or disease progression. Finally the AAEM concluded that "information ...is insufficient to make conclusions about the usefulness of this form of sensory testing at the present time."[22]

Position Statements, Practice Parameters, and Expert Opinions

The American Academy of Neurology's (AAN) Subcommittee on Therapeutics and Technology Assessment published a review of QST in the March 2003 issue of the journal *Neurology*. Part of this review looked at data on Neurotron's CPT device in diabetic neuropathy. This review raised concern over whether QST can be used by itself to diagnose diabetic neuropathy. The overall conclusions were centered on QST in general and not CPT specifically. The Subcommittee concluded that "QST is a potentially useful too for measuring sensory impairment for clinical and research studies. However, QST results should not be the sole criteria used to diagnose pathology."(Shy et al, 2003).

The AAN, AAEM, and American Academy of Physical Medicine and Rehabilitation published a practice parameter on the use of electrodiagnostic studies in the evaluation of carpal tunnel syndrome (CTS) (Jablecki et al, 2002). This article reviewed the indications and recommendations for electrodiagnostic studies in CTS patients. Nerve conduction studies and needle EMGs were discussed and various techniques recommended, but neither CPT nor v -NCT were mentioned in this practice parameter. The article did include a disclaimer that stated its intent was not "to include all possible proper methods of care for a particular clinical problem…neither (was) it intended to exclude any reasonable alternative methodologies."[23]

The Texas Worker's Compensation Commission wrote to CMS on September 12, 2001 and stated:

"The Spine Treatment Guideline Revision Workgroup review of CPT, a type of sensory conductive test, indicated that there was supporting literature for its effectiveness in some medical conditions but there was little evidence to warrant its use for musculoskeletal conditions. However, staff's review of the literature supplied by commenters supported the efficacy for CPT testing for peripheral neuropathy that is not clinically detectable through sensory nerve conduction velocity (NCV) studies. Staff's review of the literature also supported the efficacy of CPT testing for the evaluation of radiculopathies and as an appropriate diagnostic tool for the quantitative measure of the functional integrity of sensory nerve fibers."

CMS sought out the opinion of clinical experts in the field of peripheral neuropathies. The requestor provided CMS with a list of experts and we contacted three from this list. CMS also identified other experts not referred to us by the requestor. All were practicing physicians with knowledge of CPT testing and expertise in treating patients with various peripheral neuropathologies. None felt that CPT had a role as a sole diagnostic test in the work-up of a patient with suspected neuropathology. Even in purely sensory conditions the experts all said that CPT testing should be done only if other, standard diagnostic modalities were equivocal or non-diagnostic. All of the experts referred to us by the manufacturer felt that CPT had a role in the work-up of some patients with peripheral neuropathies. The experts we contacted on our own were less uniform in their support of CPT. Finally, none of the experts contacted were familiar with the Medi-Dx 7000 v-NCT device.

As part of the original consideration by CMS of s-NCT, the American Association of Clinical Endocrinologists (AACE) wrote to CMS on November 26, 2001 in support of Medicare coverage of s-NCT. The AACE believed that it was reasonable to perform s-NCT in some diabetic patients because it (s-NCT) may detect neuropathy earlier than NCS and could be used for monitoring improvement or worsening of diabetic polyneuropathy. As part of this reconsideration, CMS contacted the AACE for an update on their position and we spoke with one of the signers of that November 26, 2001 letter, Rhoda Cobin, MD (who at the time the letter was written was the president of AACE and who now is the AACE's immediate past-president). Dr. Cobin reiterated the AACE's support of s-NCT for the monitoring of diabetic polyneuropathy. When asked how s-NCT could guide patient management beyond currently available methods she stated that one significant benefit of s-NCT is that it can provide yet another piece of evidence to patients, evidence that may be more concrete than other findings (i.e., above and beyond what could be argued to be more abstract values such as hemoglobin A1c level), that end-organ damage is imminent. This, in turn, can increase a patient's compliance with therapy. Dr. Cobin, however, did not give an example of how s-NCT, by itself, affects patient management any differently than can be done with current, standard therapy.

CMS did not identify any other practice parameters or clinical guidelines from relevant professional healthcare organizations concerning the use of s-NCT. This included a search of the Agency for Healthcare Research and Quality clearinghouse.

Public Comments

In response to our review of this issue, we received two letters in support of the Neurometer®, both from physicians practicing in the field of Endocrinology and both in support of the device's use for the evaluation and management of diabetic polyneuropathy. No clinical data were submitted with either letter. We also received 5 letters in support of the use of the Medi-DX 7000.

VI. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act. § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the items or services and their expenses must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member[."] § 1862(a)(1)(A).

As previously mentioned in this decision memorandum, sensory nerve conduction threshold testing falls within a Medicare benefit category of a diagnostic test. In addition, no statutory provision specifically precludes payment. We have fully examined the medical and scientific evidence submitted with the request for a national coverage determination as well as additional evidence identified by CMS to determine whether these devices are reasonable and necessary for the diagnosis or treatment of illness or injury.

The manufacturers of both types of s-NCT devices have asserted that these technologies can be used to diagnose a variety of neuropathologies and that the quantitative information provided by the tests guides patient management. In order for CMS to conclude that these devices can accomplish such goals, we should see clear evidence that: 1) each device type has conclusive diagnostic ability as supported by strong test performance (i.e., test accuracy and reproducibility),[24] and/or 2) the quantitative information provided actually affected patient management and led to an improvement in patient net health outcomes. Certainly the impact on patient management can vary depending on the nature of the device or test. Relatively simple, non-invasive tests might have a value in the initial assessment of symptomatic patients to determine if more invasive tests are warranted. s-NCT is considered by some to be such a device. However, the evidence still must demonstrate that the simpler test has an acceptable level of validity otherwise it cannot reliably predict who will need more invasive tests. CMS should also be able to determine that there are well established, population-based normative values for each device.

In regards to test performance, it is important that both sensitivity and specificity data be available. This requires an accepted reference standard ("gold standard") against which to compare the s-NCT devices. Both sensitivity and specificity are needed to evaluate a test's accuracy. An elevated level in one is often associated with a lower level in the other and that presents a situation where one finds either elevated false-negatives (in the case of a high specificity and low sensitivity) or elevated false-positives (in the case of a high sensitivity and low specificity). In cases where there is no accepted "gold standard" that can act as a reference against which to compare the s-NCT tests, then investigators would need to compare to the best reference test and, depending on the reference test and the claims made regarding s-NCT, to follow patients longitudinally to determine if the findings on s-NCT could be verified (i.e., if s-NCT values could diagnose certain conditions and there was no reference verification then longitudinal follow-up to see if these patients did indeed develop the condition would be needed). It is also important to see how reproducible a test is in the same patient with the same observer (intra-rater) and in the same patient with different observers (inter-rater) reliability. Large variability in either intra- or inter-rater reliability would call into question the accuracy of the test and the ability to follow patients' disease course or response to treatment over time.

Normative values are also important. The manufacturers of each type of device assert that the test values from their respective device are indicative of sensory dysfunction. If this is the case, there must be a set of normal values for healthy individuals. Since healthy individuals comprise a wide group in terms of age and sex, the range of normal values may be large. As such, normal values are best derived from a population-based study, preferably from a group of patients who were confirmed not to have any neurologic abnormality that could confound the results. Small samples of healthy individuals may not be truly representative of the population at large, and large studies that do not exclude patients with neurologic disorder may yield values that are not truly normal.

Finally, the information used to support the above information should be drawn from well-designed studies. The studies should be designed to minimize systematic error such as selection bias, observer bias and confounding.[25] While random error can be accounted for in statistical analysis, systematic error unpredictably influences study outcomes and raises concerns about the validity of any findings.

In the following, we will first address these issues as they pertain to the evidence reviewed concerning the current-output type of s-NCT device (e.g., CPT, PPT, PTT tests) and then, as they concern the voltage-input type of s-NCT device (v-NCT).

Sensory-Nerve Conduction Threshold Testing using the Current Perception Threshold (or Pain Perception Threshold and Pain Tolerance Threshold) Test

The cornerstone of any study investigating diagnostic ability or utility in improving patient health outcomes is a design that minimizes systematic error. The majority of the studies reviewed herein did not provide adequate information concerning how patients were selected. It is important for authors to disclose fully how the studied patients were chosen (e.g., did they come from a specialty clinic, were they referred for the study, how were those referrals derived, were they consecutively enrolled and then subjected to inclusion/exclusion criteria, or was the pool of subjects first screened for inclusion/exclusion criteria and then enrolled). Likewise, if there were constraints placed on enrolled subjects (e.g., inclusion/exclusion criteria) these need to be fully noted. As noted in the Summary of Evidence section of this decision memorandum, the literature reviewed consistently failed to provide detailed information on patient selection.

Another systematic error that must be minimized in a well-designed study is observer bias. Blinding of the observer and patient as to what test is being done, and to the purpose of the study if possible, would lower the chance for such bias. Before addressing this further, however, we must clarify the difference between masking the observer and patient and the CPT device paradigm where the test is administered in either a single or double blind manner.[26] The testing is generally done in such a manner that the actual amplitude of the frequency being delivered is unknown to the patient and, in more recent studies, the observer as well. This does not mean that the observer is unaware of the frequency being delivered nor does it mean that the observer is unaware of the patient's diagnosis or the study's hypothesis. In studies where healthy controls are compared to patients with a disease, knowing which group the patient is in can affect how the observer administers the test. Even if the bias is unconscious, errors can occur if certain groups are given more instruction or encouraged more than another group. To minimize such potential systematic error, the observer should be masked to the patient's diagnosis, to the results of other studies, and, optimally, to the study hypothesis. We were unable to identify any published, "double-blinded" studies of these devices.

Confounding also should be minimized. When studying CPT for a certain condition, or when investigating it in normal subjects, the presence of conditions that could affect the measurements (outside of the condition being studied) should cause a subject to be excluded from the study. In some articles this was done, however, not all articles were diligent in controlling for confounders. In many studies there was no confirmatory physical exam while in others it was not clear that patients with other possible sources of neuropathy (e.g., diabetes, alcohol consumption) had been excluded.

CMS also has concerns regarding whether or not there are accepted, normal CPT values. A review of the various studies, as well as the normative values the requestor presented to CMS, demonstrates that there is no clear consensus on the effect of aging or gender on CPT values at different body sites or at the three generally tested frequencies. A look at the table the authors provided CMS containing normative values from various countries shows the mean values were accompanied by very large standard deviations which calls into question the confidence one can place in the reported mean values. In addition, the available normative data do not come from a systematic program for their determination. With the exception of the Takekuma study, the sample sizes from which these normative values were derived are small and it is not clear that the patient samples studied were truly representative of the larger normal population. Takekuma et al (2000) studied CPT values in a community-dwelling setting but did not confirm that the normative values were derived from neurologically normal subjects. Thus, although their sample size was large, we do not believe the results truly reflect normal values if the sample included patients with any clinical neuropathy. Combined, these issues lead CMS to believe that normal reference values for CPT are not well established. Furthermore, many studies compared CPT findings in patients with neuropathy to a small group of controls rather than a large, population-based sample.

CMS' concern with the quality of the normative data is illustrated by the manufacturer's description of how the normative USA values they provided us were derived. These values were culled from various studies, some published and some unpublished. This is problematic because it is not clear that these studies were conducted in such a manner that population-based, normal values could be derived with confidence. The manufacturer also stated that various doctors around the country provided normative CPT data that were gathered in the course of screening patients. This is especially problematic since there is no clear indication that the patients from these doctors' personal observations were truly neurologically normal as defined by being without risk factors, symptoms, and having had a normal neurological examination.

The available literature also does not adequately address the validity of CPT, PPT, or PTT testing. Many of the articles do report sensitivity values, but in most cases these values are not verifiable and not derived from studies with strong methodologies. In most cases, also, no specificity data are reported. In many cases CMS was unable to independently verify the sensitivity data presented, requiring us to take the author's values at face value. For one article (BenEliyahu et al, 2000) the authors reported the sensitivity of CPT testing in diagnosing intervertebral disc disease was 84%. They did not present a specificity value. CMS was unable to independently verify this 84% sensitivity. Indeed, when we used the data the authors presented on diagnoses made by the comparison standard MRI and by CPT we derived a sensitivity of 91% but a specificity of 17%. For another article (Katims, Patel, et al, 1991) the authors reported that CPT testing was a “sensitive” technique for obtaining quantitative measurements in CTS. They did not provide an actual sensitivity value, but CMS was able to extract enough information from their report to calculate a sensitivity of 62.5% and a specificity of 12.5%. These are relatively poor test performance values. Overall, there was no article where CPT was compared to an accepted reference standard in a group of patients with minimized selection bias and good observer masking. Thus, CMS cannot determine what the true sensitivity and specificity values are for CPT testing in any neuropathologic condition.

It is also important to know that the test results are reproducible (e.g., intra-rater and inter-rater variability). The study by Park, Wallace and Schulteis (2001) noted that the repeatability of CPT testing at each frequency was large with confidence intervals that were 4.5 to 17 times higher than for the other measured sensory tests. Mironer and Somerville (2000) noted an intra-individual variation for PPT of 46% and for PTT of 18%. These authors did not provide information on the intra-rater variability for CPT. In addition; Pitei et al (1994) noted that CPT reproducibility was better in control patients than in patients with diabetic neuropathy. The correlation of variation in controls ranged from 6.4-27.7% while in diabetic neuropathic subjects the correlation of variation was 28.4-52.3%. Pitei and co-authors also noted that the reproducibility of CPT measurements was better at the 2000 Hz frequency and decreased as the stimulus frequency decreased. Thus, the available data raise doubt about the reproducibility of CPT testing.

One of the other purported uses of s-NCT testing is its ability to aid in patient management. To substantiate this claim, studies that are simply individual patient scenarios are of limited value. Most reliable are studies that demonstrate in a group of patients how information provided by the test actually led to positive changes in patient management. Uniformly, the literature failed to do this. Many of the studies suggested situations where such information could be useful, but none definitively showed that CPT readings actually guided patient management in a positive direction. One study (Mironer and Somerville, 2000) was undertaken to see if success in a spinal cord stimulator trial could be predicted using CPT. Although this might be a useful function for CPT, the study had poor intra-rater reliability, patient selection biases, and failure to control for confounders making it impossible to draw a conclusion on CPT use in guiding patient management.

In three articles CPT was used only as a research tool in the investigation of the effect of various forms of analgesia or anesthesia (Angst et al 2001, Liu et al 1995, Rendell and Bamisedum 1992). These studies failed to demonstrate that CPT has utility in the diagnosis and treatment of a pathologic condition.

The manufacturer has made the point to CMS that testing at the three frequencies (5, 250, and 2000 Hz) allows the device to provide information on the three different nerve fiber types (C, alpha-delta, and alpha-beta). If this were true then one would expect correlation of the CPT device with other QSTs that are known to affect each fiber type. However, not all studies support this assertion. Pelmear and Kusiak (1994) noted that vibration threshold correlated with CPT testing at 250 Hz. The 250 Hz stimulus is supposedly selective for the alpha-delta fibers, which do not serve vibration (vibration is served by alpha-beta fibers), but serve cold sensation and the first component of pain. Pitei et al (1994) also reported that there were a number of patients with abnormal vibration testing but normal 2000 Hz CPT as well as abnormal warm and cold testing not detected by the 5 or 250 Hz stimuli. Finally, in the article by Tay, Wallace and Irving (1997) touch, pinprick and cold sensation were more affected by the lidocaine spinal anesthesia than the different CPT values. If, as suggested, CPT is more sensitive to changes in the nerve fibers than other QSTs, then changes in such tests as touch, pinprick, and cold should be accompanied, if not preceded by, CPT changes. These conflicting findings, therefore, call into question the neuro-selectivity of CPT testing.

The study by Veves et al (1991) provided histologic evidence that called into question the neuroselectivity of CPT testing. In that study strong correlation was found between nerve fiber density in the sural nerve and conduction velocity and action potential on NCS testing. However, even at the 2000 Hz level of CPT testing, which one would have expected to show some abnormalities related to loss of myelinated nerve fibers, no changes were noted.

The manufacturer of the CPT device has asserted to CMS that the device can be used as a first line diagnostic tool in patients with various neuropathologies. We contacted numerous experts, including those who were referred to us by the manufacturer, and they all stated that they do not consider CPT testing a first line diagnostic modality. The consensus amongst all the experts queried was that CPT testing might be useful only as a second line test when other more standard tests were inconclusive. Indeed, one of the articles reviewed herein summed up this issue well. Donaghue et al (1995) stated that in their study of diabetic neuropathy that the high variability of CPT and VPT demonstrated that one measurement of either test is not sufficient to diagnosis diabetic neuropathy and that to accurately diagnosis this condition using QST more than one type of QST should be employed.

The letters CMS received concerning the two s-NCT devices were supportive (i.e., CPT or v-NCT). However, the positive comments provided were based on personal observation and were not accompanied by additional evidence. The Texas Worker's Compensation Commission wrote to CMS to state their staff's conclusions regarding CPT testing. The literature they reviewed and the manner in which such evidence was critiqued, however, was not stated. The only formal technology assessment of CPT was that done by the AAEM. This well-researched assessment, with established criteria for evidence inclusion and for evidence analysis, was not supportive of the technology. Finally, the AACE, in a letter to CMS in November 2001, stated their support of CPT testing in the assessment of diabetic patients. This was followed up by a phone discussion between CMS and Dr. Rhoda Cobin, one of the signers of that letter. In that call, Dr. Cobin reiterated the AACE's support of CPT testing and stated that CPT could provide concrete evidence of end-organ damage that increase a patient's compliance with their diabetic treatment. CMS has been unable to locate evidence that supports this assertion that evidence of end-organ damage will improve a patient's compliance with therapy.

In summary, CMS has analyzed the available literature concerning the current output type of s-NCT device (which encompasses CPT, PPT, and PTT testing). This analysis leads CMS to conclude that the device's ability to accurately diagnose various neuropathologies is not proven. The evidence is not adequate to conclude that s-NCT with CPT is reasonable and necessary to diagnose sensory nerve or root abnormalities.

Sensory-Nerve Conduction Threshold Testing using the Voltage-Nerve Conduction Threshold (v-NCT) Test

Two studies (Cork et al, 2002 and Saleemi et al, 2002) using v-NCT were identified and reviewed. The study by Cork et al had several significant methodologic flaws (e.g., patient selection and recruitment methods were unclear as were whether observers were masked) that made drawing a conclusion from the study impossible. In addition, Saleemi et al did not directly investigate the use of v-NCT. They used v-NCT as part of the diagnostic work-up, but without comparison to a reference standard. In addition, there was no data presented that demonstrated that well-standardized normal values have been established for this device. As such, the evidence is not adequate for CMS to conclude that s-NCT using v-NCT is reasonable and necessary for diagnosing sensory nerve or root abnormalities.

DECISION

Based on the evidence as a whole, CMS concludes that the use of any type of s-NCT device (e.g., “current output” type device used to perform CPT, PPT, or PTT testing or “voltage input” type device used for v-NCT testing) to diagnose sensory neuropathies or radiculopathies in Medicare beneficiaries is not reasonable and necessary. Therefore, CMS intends to maintain its national noncoverage policy for sensory-Nerve Conduction Threshold testing.

Appendix 1

List of Abbreviations

AACE	American Association of Clinical Endocrinologists
AAEM	American Association of Electrodiagnostic Medicine
AAN	American Academy of Neurology
ChE	cholinesterase
CMS	Centers for Medicare and Medicaid Services
CPT	current perception threshold
CRPS	chronic regional pain syndrome
CTS	carpal tunnel syndrome
EMG	electromyography
HAVS	hand arm vibration syndrome
MRI	magnetic resonance imaging
NCS	nerve conduction study
ND-NIDDM	newly diagnosed - non-insulin dependent diabetes mellitus
NDS	neuropathy disability score
NIDDM	non-insulin dependent diabetes mellitus
NSS	neuropathy symptom score
PPT	pain perception threshold
PTT	pain tolerance threshold
QST	quantitative sensory testing
SCS	spinal cord stimulator
s-NCT	sensory nerve conduction threshold
SWM	Semmes-Weinstein monofilament
TPT	thermal perception test
v-NCT	voltage nerve conduction threshold
VPT	vibration perception threshold

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1 Forced-choice testing describes a situation where a patient must give a response to a stimulus before the next stimulus us provided. Thus, they are “forced” to respond (or make a choice) with each stimulus.

2 CMS queried the manufacturer on the source of the USA normative data. The manufacturer stated that healthy normative CPT data was culled from various published and unpublished studies. In addition, various doctors around the USA provided the manufacturer with normative CPT values gathered in the course of their screening participants for studies unrelated to the direct investigation of CPT.

3 This is an important issue since the vast majority of the studies reviewed herein, and, indeed, the vast majority of conditions for which the test is used, involved peripheral neuropathies affecting the extremities.

4 This study, as well as the 1986 study by Katims et al (described in the paragraph following), comprised part of the previously discussed USA normative data supplied to CMS by the manufacturer.

5 The abstract for this article stated that s-NCT was performed on 54 normal subjects but in the results section the authors stated the test was done on 44 normal subjects. There was no discussion about this discrepancy.

6 Dyck PJ. Detection, characterization, and staging of polyneuropathy: assessed in diabetics. *Muscle and Nerve*. 1988;11:21-32.

7 Masson and Boulton, 1991, p.S63.

8 Dyck PJ et al. Human diabetic endoneurial sorbitol, fructose, and myoinositol related to sural nerve morphometry. *Annals of Neurology*. 1980;9:590-596.

9 Veves A et al. Painful neuropathy in diabetics patients with or without foot ulceration. *Diabetes Care* 1993;16:1187-1189.

10 Dyck PJ. Detection, characterization, and staging of polyneuropathy: assessed in diabetics. *Muscle and Nerve*. 1988;11:21-32.

11 To assess reliability all tests were repeated once by the same investigator who conducted the test initially. The inter-test interval ranged from 1 to 60 days.

12 Katims J. Current perception threshold mis-evaluation. *Journal of Occupational Medicine* 1995;37:790-791.

13 Franzblau A, Werner R, Johnston E, et al. Author's reply. *Journal of Occupational Medicine* 1995;37:791-793.

14 In their analysis, the authors took the results for the diagnostic staging for the 138 subjects and put them into a grouping (sensory cluster). They then used a discriminate analysis in reviewing these clusters. What is meant by this is that any outlying values are handled such that they do not drive the analysis. The following is an example of a cluster analysis with discriminate analysis: one desires to draw up a sensory value for the fingers on a patient's hand so a sensory value (by whatever means) is determined for each finger. These values can then be "clustered" together to come up with an overall value for the hand. If the values from one of the fingers is very different then that value can be removed as art of a "discriminate analysis" so that one finger does not drive the cluster.

15 In organophosphate pesticide exposure the ChE level decreases,

16 CRPS is a neuropathic condition characterized by sensory, motor, and autonomic dysfunction usually in the distal extremities and not following a dermatome distribution.

17 Stanton Hick M, Janig W, Hassenback S, et al. Reflex sympathetic dystrophy: changing concepts and taxonomy. *Pain* 1995;63:127-133.

18 Allodynia refers to pain from non-noxious stimuli. An example is pain produced by the touch of clothes on a person's body.

19 Fabry's disease is an x-linked disorder caused by a deficiency in the lysosomal enzyme alpha-galactosidase. It manifests as episodic excruciating burning pain in the extremities, skins lesions, cardiac, renal, and gastrointestinal vascular abnormalities.

20 Piriformis syndrome occurs when the piriformis muscle irritates the sciatic nerve causing pain in the buttocks and referring pain along the course of the sciatic nerve.

21 Technology Review: The Neurometer® Current Perception Threshold. *Muscle & Nerve* 1999:Supp. 8; S250.

22 Ibid.

23 Jablecki et al, 2002, p.1592.

24 A diagnostic test's accuracy reflects how well the test detects the presence of disease (e.g., sensitivity) and how good it is at not detecting disease in the absence of disease (e.g., specificity). Reproducibility of a diagnostic test reflects how good it is at measuring the same value on repeat measurements when the value truly stays the same (e.g., precision).

25 Selection bias occurs if the way in which cases and controls are selected is such that a difference can be observed from the outset. Observer bias occurs when the person taking measurements or making observations of the cases and controls is able to introduce his/her own preconceived notions into the measurement process. Confounding occurs when more than one factor can account for an outcome and both factors are not taken into account in the study design.

26 Note: The manufacturer has told CMS that the test is done in a double-masked fashion. A review of the literature reveals that early studies, primarily those published before 1992, utilized the CPT test in a single masked fashion.

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